# Acute Alcohol and Cognition:

# Remembering What It Causes Us to Forget

Candice E. Van Skike[1], Charles Goodlett[2], and Douglas B. Matthews[3]

1. Department of Cellular and Integrative Physiology and The Barshop Institute for Longevity and Aging Studies, University of Texas Health Science Center at San Antonio, TX 78245

2. Department of Psychology, Indiana University-Purdue University Indianapolis, Indianapolis, IN 46202

3. Division of Psychology, University of Wisconsin – Eau Claire, Eau Claire, WI 54702

Please address all correspondence to:

Douglas B Matthews, PhD

Division of Psychology

University of Wisconsin – Eau Claire

Eau Claire, WI 54702

matthedb@uwec.edu

This is the author's manuscript of the article published in final edited form as:

Van Skike, C. E., Goodlett, C., & Matthews, D. B. (2019). Acute Alcohol and Cognition: Remembering What It Causes Us to Forget. Alcohol. https://doi.org/10.1016/j.alcohol.2019.03.006

**Abstract**

Addiction has been conceptualized as a specific form of memory that appropriates typically adaptive neural mechanisms of learning to produce the progressive spiral of drug-seeking and drug-taking behavior, perpetuating the path to addiction through aberrant processes of drug-related learning and memory. From that perspective, to understand the development of alcohol use disorders it is critical to identify how a single exposure to alcohol enters into or alters the processes of learning and memory, so that involvement of and changes in neuroplasticity processes responsible for learning and memory can be identified early on. This review characterizes the effects produced by acute alcohol intoxication as a function of brain region and memory neurocircuitry. In general, exposure to ethanol doses that produce intoxicating effects causes consistent impairments in learning and memory processes mediated by specific brain circuitry, whereas lower doses either have no effect or produce a facilitation of memory under certain task conditions. Therefore, acute ethanol does not produce a global impairment of learning and memory, and can actually facilitate particular types of memory, perhaps particular types of memory that facilitate the development of excessive alcohol use. In addition, the effects on cognition are dependent on brain region, task demands, dose received, pharmacokinetics, and tolerance. Additionally, we explore the underlying alterations in neurophysiology produced by acute alcohol exposure that help to explain these changes in cognition and highlight future directions for research. Through understanding the impact acute alcohol intoxication has on cognition, the preliminary changes potentially causing a problematic addiction memory can better be identified.

**Abbreviations**

| | |
|---|---|
| BAC | Blood alcohol concentration |
| IEGs | Immediate early genes |
| EPSCs | Excitatory postsynaptic currents |
| LTD | Long-term depression |
| LTP | Long-term potentiation |
| NOR | Novel object recognition |
| STEP | Striatal-enriched protein tyrosine phosphatase |

**Key Words**
Ethanol
Acute alcohol
Learning
Memory
Cognition
Hippocampus

## PROLOGUE

Understanding why and how an individual transitions from being a social drinker to one with an alcohol use disorder (AUD) is a central issue currently facing alcohol research. Identifying the sources of underlying individual differences in the progression to an AUD and addiction is a complex challenge, but such understanding is crucial to the development of effective interventions for AUD treatment and prevention. From a biological psychology perspective, ongoing behavior is mostly dependent on the functional interactions between various neurocircuits that engage different brain regions that are involved in distinct or dissociable functions. While many behavioral classifications have been developed to explain this dynamic interplay between neurocircuits of different brain regions, cognition, i.e., learning and memory, has been a prevalent framework to understand how ongoing behavior is the result of this functional interplay and therefore can be informative in understanding some aspects of the development of an AUD.

As an illustration, it has long been hypothesized and later confirmed that many animal species have a predisposition to use particular cognitive strategies to learn tasks and there are species-typical hierarchies for behavioral strategies that depend both on sensory-perceptual biases and attentional-cognitive processes. For example, behavioral studies have shown that animals will use allocententric information to learn tasks instead of egocentric information (Tolman, 1948; O'Keefe & Nadel, 1978; Matthews & Best, 1997). However, if an animal is over-trained, the use of egocentric information will often supersede the use of allocentric information (O'Keefe & Nadel, 1978). This work demonstrates a functional hierarchy of cognition exists to organize and guide behaviors that can be both relatively stable and change predictably with experience based on learning processes. The organization and neural

architecture of species-typical hierarchies of cognitive strategies can also be revealed by experimental dissociation studies, extending from approaches that have advanced the understanding of neural systems mediating declarative and non-declarative long-term memory (Squire, 2004; Bechara et al., 1995). These experimental approaches not only demonstrate that specific structures or circuits can be selectively essential for specific types of cognitive processes (and not others), but also that manipulations that target a specific brain structure and interfere selectively with one type of cognitive function can lead to compensation or hierarchical reorganization that favors an alternative cognitive strategy. For example, the hippocampal region is essential for allocentic information use whereas the striatal region supports egocentric information use. Consistent with this, experimental manipulations that impair hippocampal function, and consequently degrade the use of allocentric information, lead to augmented use of egocentric, striatal cognitive functions.

It has been proposed that one mechanism by which alcohol addiction can lead to the development of an alcohol use disorder is by directly altering the cognitive strategy that is preferentially used. Specifically, it is hypothesized that alcohol first impairs the function of the limbic circuit comprised of the hippocampus, prefrontal cortex, nucleus accumbens and ventral tegmental area thereby facilitating a progressive shift in executive control of behavior from goal directed to compulsive drug use. This change in control corresponds to a concomitant loss of prefrontal cortical regulation to a predominant control by the dorsal striatum that is associated with plasticity that shifts behavioral regulation via midbrain dopaminergic ventral striatal systems to dorsal striatal systems (for initial review see Everitt & Robbins, 2005). Learning occurring during repeated alcohol use in which behavior becomes increasingly controlled by context and the reinforcement history associated with alcohol would then facilitate activity in

specific striatal circuits namely the functionality of the dorsal medial striatum would be degraded while the dorsal lateral striatum would be enhanced. Such a shift in brain region dominance would lead first to the use of egocentric information instead of allocentric information followed by habitual responding instead of goal directed responding. Once habitual responding has been strengthened in the presence of alcohol-related cues, the individual is at risk for development of an alcohol use disorder. See Figure 1.

If this overarching framework detailing the importance of cognition in the development of an alcohol use disorder is correct, it is important to understand the history of alcohol's effects on cognition. By exploring the archives of how alcohol impacts cognition, we can gain insights into pathways that can be explored to understand the development of alcohol use disorders.

## INTRODUCTION

Alcohol use produces a variety of changes in ongoing behavior that range from slight motor impairments to respiratory depression that potentially leads to death. A full accounting of the nature and extent of the various effects of alcohol requires cross-disciplinary understanding, including genetic, molecular, systems neuroscience, previous experience with the drug, epidemiological, developmental, and social factors. When investigating a specific functional change produced by ethanol, researchers much also consider changes in function(s) from any one or more of the other levels or perspectives when trying to account for the constellation of impairments frequently observed. From that perspective, a central thesis of this review is that the role of cognition and of alcohol's effect on cognition, specifically learning and memory, can directly impact or mediate effects described at other levels of analysis, and a full accounting of

the neurobiological and psychosocial effects of alcohol (from genes to behavior) is incomplete without incorporating cognitive effects in understanding the actions and outcomes of alcohol use.

Learning and memory has long been a core problem and focus of research for many academic disciplines. Recently, though, it has been strongly argued that addiction, including addiction to alcohol, needs to be understood in relation to altered or impaired learning and memory (Boening, 2001). It has been argued that addiction might in fact be a specific form of memory itself, i.e., an addiction memory (Mello, 1972; O'Brian et al., 1998). More recently, the addiction process has been thought to involve persistent, maladaptive drug-associated memories that maintain drug seeking and taking in the face of long-term adverse outcomes (Milton & Everitt, 2012). From this perspective, two factors causing, strengthening, and maintaining addiction are the initial inhibition of limbic-system based memories and the enhancement of sensorimotor system based memories. In this view aberrant learning processes in which drug-associated stimuli become associated with the hedonic effects of drugs come to acquire control over drug-seeking and drug-taking responses for drugs (Everitt & Robbins, 2005; Everitt and Robbins, 2016). As such, understanding and manipulating these aberrant drug-related memories provide a novel approach to more effective treatment of substance use disorders and addiction (Milton & Everitt, 2010). It is critical to understand the neural circuitry and neuroplasticity underlying both typical and aberrant drug-associated learning, and to understand the bidirectional interactions between mechanisms of learning and memory and drugs of abuse, including alcohol.

The current work systematically reviews the historical and recent research investigating the effects of acute alcohol exposure on different types of memory systems. While it is recognized that differences between the effects of acute and chronic ethanol on cognition will exist, the current review is limited to acute alcohol exposure, due to the large amount of literature

and need for establishing a framework to compare to the effects of chronic ethanol. This review covers both the animal and human literature by using brain region as a basis of comparison, recognizing the limitation that this regional brain approach may not give adequate emphasis on multiple distributed, connectional systems that are involved within or between different brain regions. However, by identifying common actions or similarities of effects on specific brain regions across species, the intent is to highlight shared neurobiological mechanisms and important areas for future directions of research. Given the scope of the work in this area, we have attempted to cast a wide, historical net, but acknowledge that some important work may be omitted or overlooked due simply to the large scope of the problem. We believe, however, the emphasis on historical context is important in that knowing where the field has been can help illuminate where our research efforts should go.

## Hippocampus

Impairment of Spatial Cognition by Brain Lesions:

A wealth of research has shown that the hippocampus and related structures are intimately involved in cognition, including learning and memory. This research was galvanized by the publication of Scoville and Milner describing the cognitive effects following the bilateral removal of large portions of the hippocampus (and other medial temporal structures) in H.M. (Scoville & Milner, 1957). H.M. (Henry Molaison) was born on February 2, 1926 and died December 2, 2008. In early adolescence, H.M. developed progressive, severe, medically intractable epilepsy, leading William Scoville to perform bilateral surgical removal of large portions of his medial temporal lobes. The surgery reduced the epileptic seizures, but it produced the unintended consequence of profound anterograde amnesia. Based partially on findings in

H.M., it was proposed that the removal of H.M.'s hippocampus produced the cognitive deficits (for an overview, please see Corkin, 2002). Over the last 40 years, experimental studies in non-human primates involving bilateral lesions of medial temporal lobe structures have confirmed that memory impairments evident in H.M. and other amnestic patients can be modeled (Mishkin, 1978; Zola-Morgan and Squire, 1985), but the specific nature and types of impaired memory, the specific medial temporal lobe circuitry involved, and the relationship to human amnesia is still actively pursued (Murray and Wise, 2010). Given the importance of the hippocampal formation in learning and memory and the belief that alcohol impairs memory, the impact of acute alcohol on hippocampal-dependent learning and memory has received extensive attention. The overall conclusion from this literature is that acute alcohol exposure produces selective impairments in hippocampal-dependent memory due to a variety of factors, but most pertinently, its direct alterations in the neural function of the hippocampus.

In animal models, the hippocampus has been demonstrated to be involved in spatial learning and memory, contextual learning and memory, trace conditioning and spontaneous alternation. For example, it has been demonstrated that animals will often primarily use spatial information to organize and guide behavior in cognitive tasks (Matthews & Best, 1997; Morris, 1981; Tolman, 1948) and that one prominent factor highly correlated with the neural activity of some individual hippocampal pyramidal neurons is the spatial location of the animals (O'Keefe & Dostrovsky, 1971, O'Keefe & Speakman, 1987; for review see Best & White, 1999; Best et al., 2001). Furthermore, lesions to the hippocampus or related structures impair the use of spatial information to support learning or memory regardless of task demands (Jarrard et al., 1984; Matthews & Best, 1995; Morris et al., 1982; Packard et al., 1989). The collective summary of research results support the hypothesis that a hierarchy of information usage exists, in that

animals will often use spatial information first, even if a task is designed so that the use of spatial information is counterproductive (Matthews & Best, 1997). In addition, the hippocampus is critical for spontaneous alternation, which is the systematic variation of choices based on the spatial location of a choice (e.g. see Gross & Black, 1968).

Extending this work, research has shown that the hippocampus is intimately involved in contextual learning, perhaps related to a form of spatial memory. For example, animals trained in a standard fear conditioning task will demonstrate impaired memory when tested to the conditioned context following hippocampal lesions but not exhibit impaired memory in cue testing following hippocampal lesions (Kim & Fanselow, 1992; Maren & Fanselow, 1997; Sparks et al., 2013). There is also some evidence that the rodent dorsal hippocampus (corresponding to the primate posterior hippocampus) subserves these more cognitive functions, whereas the rodent ventral hippocampus (corresponding to the primate anterior hippocampus) is more involved in regulating stress, emotion and affect (Moser and Moser, 1998; Fanselow and Dong, 2010). Finally, evidence supporting the notion that the hippocampus is critical for spatial/contextual learning is extensive but does not completely capture all cognitive functions supported by the hippocampus. Additional examples of memory types requiring hippocampal function is trace conditioning, configural processing and pattern completion. Trace conditioning that requires the subject to remember the training information (i.e., a trace) for an intervening period prior to conditioning. This type of conditioning contrasts with delay conditioning where the training information and the conditioning event overlap. It has been consistently demonstrated that hippocampal lesions impair trace conditioning without impairing delay conditioning (Moyer et al., 1990; Solomon et al., 1986; for review see Thompson & Kim, 1996). Configural processing highlights the unique combinations that cues and/or contexts make during

the ongoing behavior of an animal. For example, in a go/no-go task Cue A in Context B can mean go while Cue A in Context C can mean no-go. The AB configural has a different meaning than the AC configural indicating the information content of cue A cannot be a simple additive stimulus. Hippocampal lesions have been shown to impair configural learning (Rudy & Sutherland, 1995; Alvarado & Rudy, 1995). Pattern completion is attuned to the notion that fragmentary information can be used to activate specific neural circuits in the hippocampus thereby providing enhanced cognition (Marr, 1971). Abstract cognition of this type has been supported by single and multiunit electrophysiological studies (e.g., Mizumori et al., 1989; Staresina et al., 2016).

Impairment in Spatial Working Memory by Acute Alcohol:

In one of the first studies investigating the effect of acute alcohol on hippocampal-dependent cognition, it was demonstrated that acute administration of 2.0 g/kg alcohol significantly reduced spontaneous alternation (Cox, 1970). This specific behavioral change established that ethanol does indeed impair cognition and suggests it might *selectively* impair cognition that is hippocampal-dependent. However, research into ethanol's specific cognitive impairments became inconclusive following a series of studies that demonstrated that although moderate doses of acute ethanol (1.5 to 2.0 g/kg) impaired contextual memory (Devenport and Carter, 1986) and reduced spatial variability (Devenport and Merriman, 1983), the drug did not seem to impair spatial cognition directly but appeared to increase general response perseveration, reduce behavioral flexibility and impair performance in reversal tasks via mechanisms other than hippocampal function in rats (Devenport et al., 1983; Devenport, 1984; Devenport and Hale, 1989) and rhesus macaques (Jedema et al., 2011 although see Wright et al., 2013). In fact, it was

eventually concluded that acute ethanol exposure does not impair spatial cognitive memory (Devenport et al., 1989). Although quite compelling, it is possible such a conclusion was reached due to an inadvertent experimental manipulation. Specifically, in these studies, subjects learned to respond on an 8-arm radial arm maze by a gradual shaping technique where food reward was initially placed on the proximal end of the reward arms and moved down the arm over days until the reward was placed at the end of the goal arm (Devenport and Hale, 1989; Devenport et al., 1989). Such a procedure might confound learning and mask specific cognitive deficits because rats would have the opportunity to not only learn spatial information but also specific cue information during the shaping procedure.

Concurrent with and following the work by Devenport and colleagues, additional investigations of the effect of systemically administered alcohol have demonstrated effects on hippocampal-dependent cognition. For example, it was found that moderate ethanol exposure (0.75 – 2.0 g/kg) impairs spatial working memory, that is, spatial memory that is useful for a specific period of time, in rodents using navigation tasks (Gibson, 1985; Givens, 1995; Hoffmann & Matthews, 2001; Rossetti et al., 2002; White et al., 1997), delayed-match-to-position tasks (Escher & Mittleman, 2004), and win-shift foraging tasks (Melchior et al., 1993). Interestingly, such effects are dose- and task- dependent in that low doses of 0.5 g/kg alcohol can actually facilitate spatial working memory under certain challenging test conditions (Rossetti et al., 2002).

Gibson (1985) specifically investigated the effect of ethanol on spatial working memory by demonstrating that a moderate dose of alcohol, 1.25 g/kg, impaired spatial working memory when animals were tested on the radial arm maze, an effect that was replicated and extended to slightly lower doses (0.75 and 1.0 g/kg) by Givens (1995). Hoffmann and Matthews (2001)

developed a more challenging spatial working memory task using the radial arm maze and demonstrated that information that was learned within a single working memory session while the rats were sober could be disrupted following an acute ethanol challenge and that the observed spatial working memory impairment was dose dependent, especially at 1.5 and 2.0 g/kg. The exact behavioral mechanism driving this reduced spatial working memory is not completely clear but is likely influenced by decreased behavioral flexibility (or novelty seeking) in rats as the dose of ethanol increases (Devenport & Merriman, 1983). This is in keeping with the previously discussed decreased behavioral flexibility associated with increased response perseveration to previously learned information (Devenport et al., 1983; Acheson et al., 2013).

Impairment in Non-spatial Working Memory by Acute Alcohol:

In addition to spatial working memory, a small set of studies also demonstrated that acute alcohol can impact non-spatial working memory, or memory that is time dependent but does not require the processing and utilization of spatial information. For example, an early report demonstrated that low (0.5 – 0.75 g/kg) doses of acute ethanol in mice impair non-spatial working memory in a task that does not requiring learning (Melchior et al., 1993; Givens & McMahon, 1997) while higher alcohol doses can impair delayed matching to sample performance in rhesus monkeys (Mello, 1971). Research results suggesting that acute ethanol impairs working memory regardless of spatial demands demonstrates that the hippocampus is a brain region significantly impacted by the drug and challenges researchers to think about more than simply specific task demands such as spatial and/or working memory.

Preliminary Cautions:

Attempts to equate specific cognitive strategies to particular brain regions are often fraught with difficulties because with such highly interconnected, parallel-distributed processing systems that characterize the brain, specific regions rarely equate 1:1 to cognitive tasks. Working memory is such an example of this conundrum. For example, H.M.'s immediate memory and digit span was relatively intact and he was able to follow task instructions during a memory session as long as disruptions and long wait times were not involved in the procedure, suggesting other brain regions are important for working memory. One such brain region is the prefrontal cortex, and the primate granular prefrontal cortex is directly interconnected with the anterior hippocampus in primates (Cavada et al., 2000) and has been suggested to store knowledge about behavior, including ordered sequences of actions and likely outcomes, along with their contexts (reviewed in Murray and Wise, 2010). The prefrontal cortex regulates the gating of information into relevant brain regions and perhaps provides a temporal register for temporary maintenance and manipulation of time sensitive information (Miller & Cohen, 2001; Baddeley, 1983; Moscovitz, 1992). Supporting the notion that working memory may have multiple forms or subcomponents that may have selective functions (e.g., visuospatial vs. phonological), and that cognitive loads imposed by different types of challenges may selectively affect specific subcomponents, acute alcohol administered in humans impairs some working memory strategies without impairing all working memory strategies (Saults et al., 2007). It is therefore critical to recognize that frameworks of single brain region to cognitive function which are frequently used, such as in this paper, do not fully represent the complexity of actual cognitive function. Fortunately, research is beginning to address the actions of acute alcohol and the neuroadaptations with chronic alcohol exposure in more cell- and circuit-based approaches to understand how the progression to alcohol use disorders relates to alcohol-induced changes in

cognitive processes (e.g., DePoy et al, 2013; Munoz et al., 2018). Where possible we have incorporated this into our efforts here.

Impairment in Spatial Reference Memory by Acute Alcohol:

Spatial working memory is a very sensitive cognitive process that can be used to investigate the effects of alcohol on cognition since the subjects need to learn spatial information that is correct for a specific time frame. Given the difficulty of tasks used to access spatial working memory, it is possible that spatial working memory impairments following acute alcohol exposure are due to the task difficulty and/or a general effect of alcohol on cognition and not specifically due to the working memory (spatial or otherwise) nature of the task. To further understand how ethanol impacts cognition that is dependent on the hippocampus, a series of studies investigating the effect of ethanol on reference memory was undertaken. Reference memory, or memory for a specific rule regardless of the temporal component, requires less behavioral flexibility and is often an easier cognitive process for animals to learn (Olton, 1983). Consequently, it is possible that acute alcohol will not impair reference memory if ethanol is producing its impairments due to task demands. However, acute ethanol exposure was found to impair spatial reference learning and spatial reference memory in a dose dependent manner from 1.5 – 2.0 g/kg ethanol in tasks that use both the radial arm maze and water maze (Matthews et al., 1995; 2002; Shimizu et al., 1998; Wright et al., 2003). Given that spatial memory is often dependent on animals using distal cues to form spatial representations of places (O'Keefe and Nadel, 1978), it is important to determine if animals under the influence of alcohol can actually perceive and use distal cues. Importantly, the spatial impairment produced by acute alcohol is not due simply to impaired visual perception (White et al., 1998).

The impairment produced by acute alcohol on spatial reference and working memory is selective in some specific situations. For instance, if a task is designed in such a way that animals can learn either spatial or non-spatial information while sober and then their memory is tested, it is found that acute ethanol (1.0 – 2.0 g/kg) impairs the use of spatial memory while actually facilitating the use of non-spatial memory, especially at moderate to high doses (Matthews et al., 1999). In addition, ethanol induced spatial memory impairments are not task specific, as similar impairments are found when animals are tested in the Morris water maze, radial arm maze, or fear conditioning chamber (e.g., Matthews et al., 1995; 2002; Melia et al., 1997). This strongly suggests that effects on motivation (food reward vs. swimming) or motor performance are not the source of ethanol's effect on hippocampal-dependent learning and memory. Furthermore, ethanol's other effects, such as ataxia, cannot be producing the spatial memory impairments for at least two reasons: First, studies that investigate the impact of alcohol on cognition that use radial arm maze tasks (Matthews 1995; 1999; White et al., 1997) typically do not use latency to perform the task as a dependent variable but instead rely on choice accuracy. Secondly, studies using the Morris water maze have demonstrated that acute alcohol exposure does not impair swimming speed at doses that would produce ataxia in other behavioral tasks (Berry & Matthews, 2004; Matthews et al., 2002). Finally, the impairments produced by alcohol are not species specific in that acute alcohol administration impairs spatial memory in mice (Berry & Matthews, 2004), rats (e.g. Matthews et al., 1999), and humans (Weissenborn & Duka, 2003).

Impairment in Contextual Memory by Acute Alcohol:

The hippocampal formation is not only critical for cognitive tasks that involve purely spatial learning and memory but also important for cognitive tasks that use contextual cues

(Sparks et al., 2013; for review see Jarrard, 1993). The role of context in learning and memory is often probed using fear conditioning, where animals are exposed to both a context and/or a cue prior to a fearful event (e.g., a footshock). Research has consistently shown that the hippocampus is critical for learning the context (Kim & Fanselow, 1992; Maren & Fanselow, 1997) while the amygdala is critical for learning of the cue (Phillips & LeDoux, 1992; for review see Fanselow & Poulos, 2005; Maren, 2008). Therefore, if ethanol does impair cognition that is based on the hippocampus, then the drug should impair contextual fear conditioning and perhaps not impair cued fear conditioning.

Research has shown that acute ethanol administered before fear conditioning results in impairments in contextual fear conditioning in adult rats when ethanol dose administered is at least 1.0 g/kg and training occurs 10 minutes following exposure; a similar effect is also found in C57BL/6J mice (Hefner and Holmes, 2007). Interestingly, the impairments produced by acute ethanol prior to training have in some cases been shown to be selective to hippocampal-dependent contextual conditioning (Melia et al., 1996; Weitemier & Ryabinin, 2003), whereas other studies have shown the impairment produced by acute ethanol may not be selective in that similar doses of ethanol administered before training also impair cued conditioning (Land & Spear, 2004) or administered pre-test can produce state dependent effects (Hunt & Barnet, 2016). However, a recent study has provided important data indicating that although ethanol administered before contextual training interferes with context retention, the reported impairment in cue retention is no longer significant if baseline freezing levels are accounted for (Broadwater & Spear, 2013). While it is true that acute ethanol can impair both contextual and cued fear conditioning, a detailed analysis of this effect demonstrates that contextual fear conditioning is more sensitive to impairments produced by acute ethanol than is cued fear conditioning. In other

words, contextual fear conditioning is impaired at lower doses of ethanol compared to cued fear conditioning (Gould, 2003). However, the differential effect on conditioning based on when ethanol is administered is complex. For example, if ethanol is administered before training in Swiss mice an increase in fear conditioning is found compared to saline tested animals.

Conditioned fear paradigms can also be used to investigate the effect of alcohol on hippocampal function without using context specifically as the hippocampal-dependent behavioral variable. For example, trace conditioning is a procedure where animals are conditioned to freeze to a cue, but the conditioning paradigm requires the animal to bridge a temporal window (i.e., a trace of time) between the neutral stimulus and the unconditioned response, and is also hippocampal-dependent (Solomon et al., 1986; for review see McEchron & Disterhoft, 1999). Interestingly, acute alcohol exposure of 0.8 and 1.6 g/kg impairs both trace conditioning and retention, which strongly suggests that alcohol impairs hippocampal-dependent cognition regardless of the task demands (Weitemier & Ryabinin, 2003). Unlike fear conditioning where the effects are variable, it appears that ethanol impairs hippocampal-dependent trace conditioning regardless of whether it is administered before or following training (Hunt et al., 2009).

Additionally, the novel object recognition (NOR) task, a version of which may be hippocampal-dependent following particular experimental manipulations (Warburton & Brown, 2015), is impaired by pre-training ethanol administration (Ryabinin et al., 2002; Swartzwelder et al., 2012). This effect is due to reduced exploration during training that carries over to testing, where mice receiving the higher dose (2.4 g/kg, but not 1.6 g/kg) of ethanol spend a similar amount of time exploring the novel and familiar objects. Importantly, these effects are not due to a reduction of locomotor activity in this group (Ryabinin et al., 2002). However, other strains of

mice show NOR memory impairments at lower (1 g/kg) doses of ethanol (Yu et al., 2013). Unlike trace conditioning, ethanol impairs NOR only when administered prior to training, and not when given after training (Ryabinin et al., 2002) suggesting ethanol might preferentially impair attentional or encoding processes in NOR.

Preliminary Conclusion and Cautions:

Animals appear to have predispositions for the use of specific cognitive strategies with hippocampal dependent cognitive strategies engaging ongoing behavior first. The allocentric cognitive strategies supported by hippocampal function provide flexible use of memory thereby facilitating behavior. This hierarchical view of cognition implies that specific types of cognition are engaged first while other types of cognition are engaged later. Acute alcohol administration impairs the use of hippocampal dependent allocentric cognition and the impairments occur at alcohol doses and corresponding blood alcohol concentrations that mirror drinking levels found in human populations. It therefore appears that one of the first systematic effects of acute intoxication is the altering of the hierarchical function of cognition whereas hippocampal dependent allocentric memory is impaired thereby facilitating the use of other type of cognitive strategies. However, it is important to remember that many drugs, including alcohol, can produce state-dependent effects whereby implied cognitive deficits are instead due to different pharmacological states between testing and training. While we believe many of ethanol's effects on cognition are not due to state-dependent effects, evidence clearly suggests state dependency can be demonstrated (e.g., Hunt & Barnet, 2016). Furthermore, we have attempted to limit our review to acute effects, however, the first exposure to a drug can led to expectations that might alter later, subsequent, effects. While difficult to investigate, implicit memory in humans (see later section) can provide some meaningful insight into this challenging issue.

Electrophysiological Correlates of Alcohol's Effect in the Hippocampus:

Although acute alcohol has been shown to impair performance in cognitive tasks that are dependent on the hippocampus, this does not demonstrate that acute ethanol produces these impairments by altering hippocampal function directly. It is therefore critical to investigate if alcohol produces effects on hippocampal neurophysiology directly that may correlate with cognitive performance, thereby providing a neural mechanism by which the drug impairs hippocampal-dependent cognition.

One of the first, and most critical findings implicating ethanol's direct effects in the hippocampus came from studies demonstrating that ethanol inhibits NMDA-activated ion currents in the hippocampus (Lovinger et al., 1989; 1990). Not surprisingly, similar concentrations of ethanol were found to inhibit hippocampal long-term potentiation (LTP; Blitzer et al., 1990). These studies have been reviewed in an excellent recent publication (Zorumski et al., 2014). These studies, and many others using LTP, strongly implicate the hippocampus as a potential site of action for ethanol's cognitive impairing effects.

Early studies designed to investigate distinct brain regions underlying ethanol's memory impairing effects used techniques to explore the expression patterns of immediate early genes (IEGs). Initially, it has been shown that the expression of IEGs such as c-Fos, is increased in a variety of brain regions due to such factors as stress, and acute alcohol selectively decreases c-Fos expression in the hippocampus (Ryabinin et al., 1995; 1997) and can increase c-Fos expression in a variety of brain regions including the amygdala and caudate-putamen (Ryabinin et al., 1997). These data suggest that c-Fos expression might be a marker for brain region activation and consequent inhibition by acute ethanol exposure. In support of this idea,

expression of IEGs is increased in relevant brain regions, such as the hippocampus, following learning paradigms (Melia et al., 1996). In addition to IEG expression being increased in brain regions associated with learning, it has been also demonstrated that acute alcohol exposure at levels that impair hippocampal-dependent learning also reduce the expression of many IEGs (for review see Ryabinin, 1998). For example, acute ethanol, at doses that block context dependent fear conditioning, significantly decreases hippocampal c-Fos expression. However, the reduction in c-Fos expression was selective in that cortical c-Fos expression was not significantly decreased (Melia et al., 1996). Acute ethanol doses that produce cognitive deficits also significantly reduce hippocampal extracellular glutamate levels but do not alter cerebellar extracellular glutamate levels (Shimizu et al., 1998), further demonstrating that acute ethanol may selectively impact hippocampal function. These data support the notion that one function of acute intoxication is to alter neurological activity in the hippocampal system thereby degrading hippocampal allocentric memory and altering the cognitive hierarchy animals use to organize and guide behaviors.

Electrophysiological studies of hippocampus and related structures have provided more direct evidence that acute ethanol degrades allocentric cognitive strategies by altering hippocampal function. Initially it was shown that acute ethanol dose dependently (0.75 g/kg to 3.0 g/kg ethanol) decreases the spontaneous activity of medial septum/diagonal band of Broca (MS/DB) neurons (Givens & Breese, 1990). Importantly for the current discussion, the inhibition of spontaneous neural activity was selective in that the spontaneous activity of lateral septal neurons was not altered. Such an inhibition of MS/DB neurons may be important because this brain region projects directly to the hippocampus and drives the hippocampal theta rhythm (for review please see Oddie & Bland, 1998), an oscillatory hippocampal field potential that predicts

learning in cognitive tasks (for review see Berry & Hoffmann, 2011). As expected, acute ethanol, at doses that impair hippocampal-dependent learning and memory, also significantly suppressed hippocampal theta rhythm (Givens, 1995; Zhang et al., 2016). These data strongly suggest that one mechanism by which acute ethanol administration alters hippocampal-dependent learning and memory is by altering hippocampal neurophysiology (for an early review see Givens et al., 2000). Indeed, this alteration may be due to ethanol decreasing levels of acetylcholine in the hippocampus (Henn et al., 1998), a reduction that is correlated with spatial memory impairments (for review see Gold, 2003). In support of this hypothesis it has recently been shown that co-administration of cholinesterase inhibitors that increase acetylcholine levels, can significantly reduce spatial memory impairments produced by acute ethanol administration (Gawel et al., 2016).

Although studies demonstrating that ethanol alters hippocampal theta rhythm highlight the hippocampus as one potential brain region underlying the deleterious cognitive effects produced by the drug, multi-unit studies are more challenging to correlate directly with ongoing behavior thereby reducing the explanatory power of these electrophysiological studies. As previously mentioned, hippocampal pyramidal neurons have been shown to increase their firing rate when an animal is in a given spatial location. These neurons, termed place cells, are thought to provide, among other things, information about the animal's location (see Best et al., 2001 for review). Therefore, if acute alcohol administration impairs spatial learning and memory, and hippocampal place cells respond to the spatial location of the animal, it seems reasonable to predict that acute alcohol should also alter the firing characteristics of hippocampal place cells in freely behaving animals. Indeed, as first reported in 1996, acute alcohol exposure at a dose (2.0 g/kg) that reliably impairs spatial, but not non-spatial, memory disrupts the spatial specificity of

hippocampal place cells in awake, freely behaving rats (Matthews et al., 1996). The disruption in the neurons' spatial specificity only occurs during intoxication and the integrity of the field is reestablished 24 hours later, which is an important finding given acute ethanol does not impair spatial memory 24 hours following exposure (Hoffmann & Matthews, 2002). Furthermore, the degradation in spatial specificity is dose and time dependent and driven primarily by a reduction in the firing frequency of the pyramidal neurons and not hippocampal interneurons (Ludwig et al., 1998; White & Best, 2000). Although the number of studies investigating acute alcohol and single unit electrophysiology in awake freely behaving animals are few, they do provide the most direct evidence to support the hypothesis that alcohol is altering cognitive hierarchies by directly impairing hippocampal function and corresponding hippocampal dependent cognition.

Potential Neurobiological Mechanism Underlying Acute Alcohol's Effect in the Hippocampus:

The mechanisms by which acute ethanol alters hippocampal neurophysiology and correspondingly degrades hippocampal-dependent cognition has yet to be completely elucidated. Based on a wealth of data, it is known that ethanol potentiates GABA inhibition and inhibits glutamate excitation in the medial septum and hippocampal brain regions (for reviews see Grobin et al., 1998; Kumar et al., 2009; Chandrasekar, 2013) suggesting these molecular effects as potential mechanisms of action. However, it is possible that ethanol produces its effect on hippocampal function indirectly via an endogenous modulator. Our laboratory, and several others, have investigated the ability of the neurosteroid allopregnanalone, a highly potent GABAergic modulator (Harrison et al., 1987; Morrow et al., 1987), to significantly degrade cognition dependent on the hippocampus due to acute ethanol administration.

Acute ethanol increases levels of allopregnanolone in a dose and time dependent manner in a variety of brain regions including the hippocampus (Barbaccia et al., 1999; VanDoren et al., 2000; Cook et. al., 2014). Interestingly, allopregnanolone formation and release in the hippocampus is not dependent on the adrenal cortex but instead appears to occur de novo (Sanna et al., 2004; Cook et al., 2014), supporting the hypothesis that ethanol induced release of allopregnanolone in the hippocampus is a critical factor underlying the cognitive impairments produced by ethanol. Initially studies replicated data demonstrating that acute ethanol administration inhibited the spontaneous activity of medial septal neurons and then demonstrated that pretreatment with the 5α-reductase inhibitor finasteride completely blocked ethanol induced inhibition of medial septal neurons (VanDoren et al., 2000). Although finasteride can impact a variety of steroid hormones (Van Doren et al., 2000; Werner et al., 2016) the initial studies motivated investigations to determine if allopregnanolone directly alters hippocampal neurophysiology; it was reported that acute allopregnanolone administration dose dependently inhibited the spontaneous activity of hippocampal pyramidal neurons and that pretreatment with finasteride blocked ethanol induced inhibition of hippocampal pyramidal neurons (Tokunaga et al., 2003). In addition, it was investigated if acute allopregananolone produced dose dependent impairments in hippocampal-dependent spatial memory in a manner similar to acute ethanol administration. Importantly, acute allopregnanolone and acute ethanol administration selectively impaired hippocampal-dependent memory (Matthews et al., 2002; Rabinowitz et al., 2014) and endogenous allopregnanolone levels correlated with ethanol-induced spatial memory impairment (Silvers et al., 2006). These data suggest that allopregnanolone increases produced by acute ethanol exposure are a viable candidate mechanism underlying ethanol induced deficits in hippocampal based learning and memory. This hypothesis is supported by findings that ethanol-

induced increases in hippocampal allopregnanolone mediate ethanol's ability to reduce hippocampal LTP (Izumi et al., 2007; Ramachandran et al., 2015). However, to date, only one preliminary report directly investigates this by first pretreating animals with finasteride to reduce allopregnanolone levels then testing spatial memory following an acute ethanol challenge. As expected, finasteride reduced the well-established impairment in hippocampal-dependent spatial memory (Morrow et al., 2003). However, a full study of the effect awaits further experimentation.

While the use of finasteride has proven successful in identifying allopregnanolone levels as a contributing factor in ethanol's effect on memory, finasteride impacts multiple neurosteroid rendering it less than an ideal pharmacological manipulation. Adrenalectomy can also significantly reduced allopregnanolone levels in brain but once again this manipulation impacts multiple neurosteroids (O'Dell et al., 2004). However, it is possible that specific genetic manipulations (in addition, please see next section of this paper) may be viable tools to explore the impact of allopregnanolone on ethanol-induced spatial memory impairments. For example, the *Srd5a1* gene encodes the enzyme 5α-reductase-1, a necessary enzyme for the formation of allopregnanolone. While there is some work demonstrating that *Srd5a1* knockout mice increase ethanol consumption (Ford et al., 2015) and have blunted ethanol effects on some components of the plus maze, the majority of ethanol's effects are not different between the knockout and the wildtype mice (Tanchuck-Nipper et al., 2015). Consequently, this knockout is not likely to be a viable tool to study ethanol's memory impairing effects. A second possibility is GABAA receptor δ knockout mice, a genetic manipulation that reduces the sensitivity to neurosteroids in both behavioral (Mihalek et al., 1999) and hippocampal electrophysiological studies (Stell et al., 2003). This strain of mouse demonstrates enhanced hippocampal-dependent trace fear

conditioning (Wiltgen et al., 2005) and blunted responses to some effects of acute ethanol (anticonvulsant effects) but normal effects to other ethanol effects (anxiolytic and hypothermia) (Mihalek et al., 2001). It is possible that GABAA receptor δ knockout mice will show blunted ethanol-induced spatial memory impairments because increases in allopregnanolone will not produce as large a behavioral impact in the knockout mice compared to the control mice. Interestingly, THIP, a neurosteroid that modulates GABAergic receptors, has a blunted spatial memory impairment and decreased LTP in GABAA receptor δ knockout mice compared to wildtype mice (Whissell et al., 2013). Based on these results it is critical to investigate if GABAA receptor δ knockout mice have reduced hippocampal dependent spatial memory impairments compared to wildtype animals.

Impact of Genetics on Acute Alcohol and Hippocampal Memory:

Understanding the genetic factors that influence the effect of acute alcohol on learning and memory is an understudied research field. To investigate genetic influences on ethanol induced memory impairments, one initial tool used was to assessed the effects of ethanol in various genetically modified mouse lines. To date, research from the Matthews' laboratory has proven relatively unsuccessful in identifying genetic factors important for ethanol's effect on cognition. Specifically, $GABA_A$ receptor α1 reduction via two different genetic manipulations or $GABA_A$ receptor γ2 knockdown did not alter ethanol induced spatial memory impairments in the Morris water maze (Berry et al., 2008; Berry et al., 2009; Werner et al., 2006). Potential genetic underpinnings of ethanol on hippocampal dependent learning and memory have also proven elusive for other laboratories. For example, $GABA_A$ receptor α5 knockout mice display similar impairments in ethanol-induced contextual fear memory compared to wildtype littermates

(Martin et al., 2011), suggesting extrasynaptic $GABA_A$ receptors do not mediate ethanol's cognitive impairing effects in the hippocampus. However, $GABA_A$ receptor α4 knockout mice display enhanced contextual learning compared to wildtypes (Cushman et al., 2011), which suggests that hippocampal-dependent learning and memory is impaired by the tonic inhibition mediated by α4δ* receptors (Moore et al., 2010; Wiltgen et al., 2005). Despite enhanced learning compared to wildtypes, α4 knockouts are more sensitive to ethanol induced contextual learning impairments (Cushman et al., 2011). This effect is likely driven by the upregulation of γ2 subunits in α4 knockout mice, which leads to enhanced ethanol sensitivity in synaptic $GABA_A$ receptor currents (Liang et al., 2008).

Genetic manipulations involving NMDA receptor (NMDAR) phosphorylation have proven to be somewhat more successful in delineating mechanisms of ethanol induced memory impairments. Ethanol conveys some of its acute memory impairing effects through inhibition of NMDA receptor -mediated LTP (Lovinger et al., 1989; Morris et al., 1986). Ethanol induced inhibition of NMDAR-mediated LTP and associated behavioral impairment has been shown to be dependent on striatal-enriched protein tyrosine phosphatase (STEP), as ethanol does not inhibit NMDA receptor excitatory postsynaptic currents (EPSCs) or block LTP in CA1 pyramidal neurons of STEP knockout mice (Hicklin et al., 2011). Furthermore, STEP knockout mice do not show ethanol -induced impairments in fear conditioning (Hicklin et al., 2011). These data demonstrate that STEP is a critical mechanism for ethanol's inhibition of NMDAR EPSCs and LTP, and fear conditioning impairments. Recently a mouse strain with a mutant GluN1 subunit that is less sensitive to the effects of ethanol has been generated and while this knockin strain has altered ethanol responsiveness to some of ethanol's effects, the effect of ethanol on cognition has yet to be investigated (den Hartog et al., 2013Zamudio-Bulcock et al., 2018).

Additionally, genetic differences in ethanol metabolism, specifically involving acetaldehyde accumulation have been shown to affect hippocampal-dependent spatial memory. Specifically, aldehyde dehydrogenase 2 (Aldh2) knockout mice showed greater ethanol induced hippocampal memory impairments in the Morris water maze and radial arm maze compared to wildtypes (Jamal et al., 2012). These impairments are likely mediated by excess acetaldehyde (Quertemont et al., 2005) that accumulates after ethanol consumption as a result of Aldh2 deficiency (Wall et al., 1997). A potentially similar effect is found in certain ethnicities. For example, a genetic polymorphism that is prevalent among East Asians resulting in increased acetaldehyde levels carries increased health risks beyond abnormal ethanol reactions and metabolism, including increased risk for certain cancers (Cai et al., 2015), coronary artery disease (Gu & Li, 2014), anxiety and depression (Yoshimasu et al., 2015), among others (for review see Vasiliou & Pappa, 2000).

Impact of Age on Acute Alcohol's Hippocampal Dependent Memory Impairments:

In the last decade, extensive research has investigated whether alcohol produces a greater cognitive impairment in adolescents compared to adults. The policy implications surrounding this are quite large given adolescents consume alcohol at alarming rates during a life-stage defined by cognitive effort, i.e., schooling. We have recently discussed this literature at length (Novier et al., 2015; section 5.2; Chin et al., 2010) and determined that it is an overstatement to conclude alcohol produces greater cognitive impairments in adolescents compared to adults.

A recent paper provides some insight into factors that might account for many of the divergent results in this literature field. Specifically, Hunt and colleagues investigated the extent to which acute ethanol impaired trace fear condition or contextual fear conditioning in both

adolescent and adult animals. They report data demonstrating that alcohol produced a greater impairment in adolescents compared to adults in trace conditioning but adults were more impaired than adolescents in context conditioning. However, the effect found in trace conditioning was state dependent whereas the effect found in context conditioning was not state dependent (Hunt & Barnet, 2016). This paper demonstrates two important issues. First, generalized state dependent impairments, not specific cognitive impairments, may underlie some of the reports demonstrating that adolescents are more sensitive to the learning and/or memory impairing effects of acute alcohol, and secondly, it is incorrect to conclude the cognitive function of adolescents is always more impaired by alcohol than adults.

Enhancement of Habit Learning following impairments in allocentric/goal learning: More than a decade ago we published a literature review where it was argued that acute alcohol is a suitable tool to study multiple memory systems (Matthews & Silvers, 2004). In making this argument, we capitalized on the work of others (e.g., Lynn Nadel, Paul Gold, Norman White and Mark Packard to name a few) to argue that a "hierarchy" of cognitive functions exist where alcohol selectively impaired one of the first engaged levels of the hierarchy, namely processes engaging the hippocampal system, therefore augmenting the importance of other, less affected, levels, e.g., the striatal system, to control behavior. We believe this may be an important factor in explaining one of the early mechanisms underlying the development of alcohol addiction.

As previously described, acute ethanol will *impair* hippocampal-dependent cognition, and, consequently, result in a *facilitation in* caudate/striatal memory (Matthews et al., 1999). In that particular study, acute ethanol decreased the use of spatial memory and increased the use of cue memory. It is interesting to speculate that acute ethanol was decreasing allocentric directed

behavior and increasing egocentric based behavior. If true, acute alcohol might produce a "cognitive switch" that reflects the underlying change in the typical hierarchy of cognitive control of learning; repeated alcohol exposure may facilitate reliance on the cognitive switch such that the compromised learning can contribute to the progression of alcohol addiction.

Research in the last decade coupled with advancements in theoretical frameworks have begun to delineate this potential cognitive switch (for an early review of this field please see Belleine et al., 2007). As outlined in a recent review of the literature (Gremel & Lovinger, 2018) three neural circuits are potentially critical to the formation of and maintenance of an AUD. While all three circuits operate in parallel during behavior, the limbic circuit, including the hippocampus, initially direct ongoing behavior. However, if damage to the limbic circuit occurs, such as the prefrontal cortex, rodents learn tasks based on the sensorimotor circuit (Balleine & Dickinson, 1998; Corbit & Balleine, 2003). In a potential extension of this to the current field of interest, as acute ethanol exposure inhibits the functionality of the limbic circuit (see above), the functionality of the associative circuit, including the dorsal medial striatum, and the sensorimotor circuit, including the dorsal lateral striatum, become more prominent. Repeated ethanol exposures over time continue to suppress the limbic circuit while facilitating the formation of habitual learning thereby shifting behavioral control to the dorsal lateral striatum and the sensorimotor loop. The individual is then at risk of an AUD as reward devaluation produced by loss of hedonic effects of the drug lose the power to inhibit habitual behavior. This theory of AUD development is supported by work showing that inactivation of the dorsal medial striatum produces responding that is insensitive to reward devaluation and is habitual (Yin, 2005a,b). Excitingly, research is beginning to support this framework by using experimental designs that focus ethanol seeking and intake on non-spatial and/or response driven cues.

The potential importance of non-spatial cues in alcohol research has been studied in work showing that cues, such as a tone or light, could enhance alcohol self-administration in operant tasks (Corbit & Janak, 2007). Indeed, habit formation and habitual responding is strengthened by alcohol exposure (Mangieri et al., 2012, for an excellent review see O'Tousa & Grahame, 2014; Corbit et al., 2012) and might reflect ethanol exposure enhancing neurological systems supporting habitual learning (Corbit et al., 2012). In support of this, it has been shown that the VTA is important for initiating Pavlovian, habitual learning (Corbit et al., 2007) with the dorsal lateral striatum and dorsal medial striatum playing a critical role in Pavlovian instrumental transfer selectivity (Corbit and Janak, 2007; Corbit and Janak, 2010; for review see Corbit & Janak, 2016). However, Pavlovian instrumental transfer tasks can be confounded with limbic circuit function (Pascoli et al., 2015). For example, reduction in ventral tegmental area activation can result in nonspecific reduced motivated responding and therefore confound a straightforward habit-response conclusion (Corit and Janak, 2007; 2010; 2016). Research utilizing self-paced instrumental tasks have highlighted the initial importance of the associative and sensorimotor circuits. Firstly, self-paced instrumental tasks has shown that both the associative and sensorimotor circuits are involved early in learning (Yin et al., 2005; 2006) and, secondly, can support sufficient learning to investigate drug related conditions (Yin et al., 2004; Gremel & Costa, 2013). Importantly, a recent paper strongly supports the notion that alcohol impacting hierarchical organization of cognition via a cognitive switch may underlie addiction. Specifically, chronic ethanol exposure (granted, a "chronic" study in a review of the effects of acute alcohol) decreases the excitable input from the orbital frontal cortex (limbic circuit) to the dorsal medial striatum (associative cortex). The result of this is an increase in the behavioral

control of the dorsal lateral striatum (sensorimotor circuit) resulting in an increase in habitual responding (Renteria et al., 2018).

The direct research from both Pavlovian instrumental transfer studies and self-paced instrumental studies demonstrating that alcohol exposure (both acute and chronic) can facilitate egocentric, habitual learning, supports the proposed cognitive switch to striatal function from cortical-hippocampal function following alcohol exposure. For example, intravenous alcohol increases fMRI activation of the striatum in humans undergoing a simulated risky gambling task (Gilman et al., 2012). In addition, low doses of alcohol do not alter caudate multiple unit activity but do alter hippocampal multiple unit activity recorded in rabbits (Klemm et al., 1976). Consequently, it is possible that acute alcohol produces a differential neurophysiological effect between striatal and hippocampal regions resulting in a "cognitive switch" from goal directed to response directed (or habit-based) behavior. The switch from goal-directed to habit-based responding can be controlled by the presence of learned contextual cues in the former switching to specific reinforcement history in the later that dynamically regulate the synaptic efficacy of orbitofrontal cortical projections to the dorsal striatum (Gremel et al., 2016; as it relates to alcohol altering orbitofrontal-mediated learning [reversal learning] in rhesus macaques please see Jedema et al., 2011). This switch involving regulation of competing circuits that control goal-directed behaviors may set the stage for the first step in risky alcohol use. Recently, this hypothesis has received strong support from studies investigating the impact of the μ-opioid system in the dorsal striatum as it relates to ethanol exposure (Munoz et al., 2018). Specifically this research team demonstrated that a short 3-day binge of ethanol selectively impaired corticostiratal μ-opioid receptor-mediated long-term depression that occurs exclusively at the synapses of anterior insula to dorsal lateral striatal inputs. This selective functional ablation of

LTD plasticity might prime at-risk individuals to seek additional ethanol consumption opportunities. While the exact neuroantamical circuit underlying the altered neurophysiology is to be determined, it does appear that cortical anterior insular neurons are critical (Munoz et al., 2018; Renteria et al., 2018). Thus it is likely that alcohol facilitates a cognitive switch from allocentric, hippocampal function to egocentric, dorsal striatal function that increases habit learning at the expense of other types of learning thereby increasing the likelihood of developing an alcohol use disorder.

From the research discussed herein, it is clear that moderate to high doses of ethanol, from 1.5 g/kg to 2.5 g/kg produce consistent impairments in hippocampal functioning. Lower doses of 0.5 g/kg have been shown to facilitate spatial working memory under challenging task conditions; but for the most part, doses between 0.25 and 0.75 g/kg do not produce reliable effects on hippocampal functioning. The effects of doses falling between these ranges are task dependent (see table 1). Overall, acute alcohol produces selective impairments in hippocampal-dependent cognition due to a variety of factors, including direct alterations in hippocampal neurophysiology. This reduction in hippocampal-dependent cognitive function facilitates the enhancement of striatal function producing habitual alcohol responding. However, despite the depth and breadth of research on ethanol's effects on the hippocampus, there are areas where gaps in knowledge remain to be bridged as well as somewhat controversial areas where a consensus has yet to be reached.

## Cerebellum

Until relatively recently the primary function of the cerebellum was thought to be motor planning and execution; however, research starting in the 1980s suggested the cerebellum had a nonmotor function, including cognition, emotion, and even social behavior and reward through

both anatomical and functional associations with the cerebrum (for reviews, see Buckner, 2013; Strick et al., 2009; Schmahmann, 2004; Roger et al., 2011; Carta et al., 2019 ). Given the interface of the motor output and cognitive function that exists in cerebellar function, it is an important brain region to explore in relation to potentially supporting a cognitive switch from allocentrentic cognition via hippocampal function to egocentric, habitual cognition via striatal function.

The importance of cerebellar circuitry in classical eyeblink conditioning, a form of associative motor learning, has been well documented in a variety of animals (Chen et al., 1996; Lavond & Steinmetz, 1989; McCormick & Thompson, 1984; Perrett et al., 1993; Skelton, 1988; Sun, 2012), as well as humans (Daum et al., 1993; Lye et al., 1988; Solomon et al., 1989; Topka et al., 1993; Chen et al., 2008). In this pavlovian procedure an unconditioned stimulus that elicits an eyeblink, such as a puff of air or periorbital shock, is slightly preceded by a tone or light conditioned stimulus and both stimuli co-terminate. Through repeated pairings, the tone, or conditioned stimulus, becomes predictive of the unconditioned stimulus, and an eyeblink will come to be elicited in response to the tone alone. As recently reviewed (Cheng et al., 2015), this paradigm has been used to study cerebellar learning deficits produced by chronic ethanol use (McGlinchey-Berroth et al., 1995; McGlinchey et al., 2005) and neonatal ethanol exposure (Brown et al., 2007; Green, 2003; Green et al., 2000; Jacobson et al., 2011; Stanton & Goodlett, 1998; Wagner et al., 2013). However, despite the implication that the cerebellar cortex is one of the most sensitive to acute ethanol administration as assessed by multiple-unit electrode activity (Klemm et al., 1976), comparatively little research has been conducted on the impact of acute ethanol on classical eyeblink conditioning. In particular, studies using task variants that can probe relative contributions of cerebellar cortex (manipulations of CS-US intervals to assess

timing control) or variants probing cerebellar- vs. cerebellar/hippocampal-dependent learning (delay vs. trace conditioning) are generally lacking.

There are some historical data in humans, but the results are mixed. In the first paper to investigate the impact of acute ethanol on eyeblink classical conditioning, acute ethanol did not impact the acquisition of the eyeblink conditioned response (Franks, 1963). In this study, participants that received ethanol had an average blood alcohol concentration (BAC) of 86 mg/dL and 80 mg/dL before and after conditioning, respectively. Importantly, all participants, including the control group (i.e., a group given a glass of soda lightly layered with 5mL of whiskey), reported that they had received ethanol. Given that certain effects of ethanol are suggestible based on alcohol-related expectancies (Monk & Heim, 2013), there may not have been a no treatment (i.e., a group that drank no solution) control group present in the study to provide a reliable baseline comparison. In contrast, a second report found that ethanol dose dependently suppressed conditioned response acquisition and blink amplitude at mean BACs of 49, and 99 mg/dL (Hobson, 1966). This dose-dependent suppression of conditioned response acquisition has been replicated in rabbits with doses of 0.375, 0.75, and 1.5 g/kg of ethanol delivered intragastrically (Hernandez et al., 1986), which produced BACs of 28.3, 82.6 and 190.2 mg/dL, respectively. However, only the highest two ethanol doses suppressed conditioned responding, with no effect at the lowest dose of ethanol. Although 0.375 g/kg ethanol produced no effect on percent eyeblink conditioned responses, animals that received this dose had greater eyeblink amplitudes at the final training session, indicating conditioned responding may be slightly facilitated by a low dose of ethanol (Hernandez & Powell, 1986).

At certain doses, ethanol also produces a state dependent effect on conditioned response extinction (Hernandez & Powell, 1986; Hernandez et al., 1986). Specifically, rabbits that

received 0.375 g/kg ethanol during both training and extinction (ethanol/ethanol) exhibited the greatest eyeblink amplitude compared to rabbits that received ethanol/water, water/ethanol, and water/water during training/extinction, respectively (Hernandez & Powell, 1986). Furthermore, rabbits that received opposing doses during training and extinction (water/ethanol, ethanol/water) had a higher percentage of eyeblink conditioned responses during extinction than the state-congruent water/water or ethanol/ethanol groups. Rabbits trained with a higher dose of 0.75 g/kg ethanol had more eyeblink conditioned responses during extinction, independently of the drug received during extinction, indicating prior ethanol exposure delayed extinction despite the ethanol-induced suppression of response at this dose (Hernandez et al., 1986). Rabbits that received the highest dose, 1.5 g/kg, during training extinguished to the same level as those that received water during training, although the ethanol-induced suppressive effect of this dose was so great that there may be a floor effect present (Hernandez et al., 1986). In sum, ethanol's effects on the behavioral manifestations of cerebellar learning appear to be dose dependent, such that low doses of ethanol facilitate certain aspects of eyeblink conditioned response acquisition, while moderate to high doses impair learning. Additionally, extinction is delayed in general during the training or extinction trials.

While the research on the overt behavioral effects of ethanol on cerebellar-dependent learning is limited, more studies have focused on the synaptic and electrophysiological changes produced by ethanol on the cerebellar learning circuits. Motor skill learning is associated with structural and functional adaptations of the cerebellar cortex, including increased synaptogenesis onto Purkinje cells (Black et al., 1990; Kleim et al., 1996; Kleim et al., 1998). Increased synaptogenesis is specific to motor skill learning, such as tasks requiring balance and fine motor skill, and is distinct from the angiogenesis caused from increased motor activity, including

running on a treadmill or running wheel (Black et al., 1990). Cerebellar plasticity also occurs in conjunction with associative learning in the eyeblink conditioning paradigm. During conditioned eyeblink training, climbing fibers relay information about the unconditioned stimulus, while parallel fibers transmit information regarding the conditioned stimulus (Thompson, 1986, 1990). Ultimately, these two fibers converge concurrently onto the same Purkinje cell and these plasticity mechanisms, including parallel fiber long-term depression (LTD) and long-term potentiation (LTP), alter Purkinje cell firing (Ito, 1989; Jorntell & Hansel, 2006; Kalmbach et al., 2010; Valenzuela et al., 2010). LTD at the parallel fiber-Purkinje cell synapse represents a well-accepted cellular mechanism underlying motor learning (Ito, 1986; Jorntell & Hansel, 2006; Valenzuela et al., 2010); however, LTD at this synapse requires concurrent activation of the parallel and climbing fibers (Chen & Thompson, 1995; Ito & Kano, 1982). In contrast to conditioned response acquisition, extinction of the conditioned response is mediated by parallel fiber LTP (Jorntell & Hansel, 2006) and climbing fiber inhibition (Medina et al., 2002).

Acute ethanol impairs the cerebellar synaptic plasticity described above (Valenzuela et al., 2010). In the case of parallel fibers, application of acute ethanol impairs the induction of parallel fiber LTD, but not LTP (Belmeguenai et al., 2008). The blockade appears to be partially mediated by parallel fiber mGluR1-activated excitatory postsynaptic currents, which are attenuated by moderately high extracellular concentrations of ethanol (50-80 mM) but not a lower concentration (20 mM) (Belmeguenai et al., 2008; Su et al., 2010).

Parallel fiber LTD can also be affected by action at the climbing fibers (He et al., 2013), and climbing fiber-related cerebellar plasticity is also affected by acute ethanol. Low concentrations of ethanol selectively impair climbing fiber evoked NMDAR-mediated excitatory postsynaptic currents (EPSCs) of Purkinje cells, but do not alter parallel fiber EPSCs (He et al.,

2013). These results indicate that altered NMDA receptor activity at the climbing fiber-Purkinje cell synapse may be the mechanism of action for low dose ethanol induced inhibition of cerebellar plasticity, as low (10 mM) and higher (50 mM) concentrations of ethanol dose dependently inhibit NMDAR-mediated EPSCs and LTD at parallel fiber-Purkinje cell synapse (He et al., 2013). However, it is likely such concentration dependent effects depend on a variety of factors including brain region. Additionally, higher concentrations of ethanol inhibit climbing fiber LTD through inhibition of mGluR1-activated EPSCs evoked by climbing fiber stimulation, which could have an indirect effect on parallel fiber-Purkinje cell LTD (Carta et al., 2006). These studies highlight the importance of glutamate in cerebellar synaptic plasticity, and suggest that the NMDA receptor may be the target for low dose ethanol LTD inhibition (He et al., 2013), while higher doses (50 mM, but not 20 mM) are required to affect mGluR-mediated LTD impairment (Belmeguenai et al., 2008; Carta et al., 2006). However, climbing fiber activation-induced complex spikes are affected by a wide range of ethanol concentrations, 10-75 mM, which reduce the area under the curve approximately 10-25%, respectively (Carta et al., 2006).

The ethanol induced changes in climbing fiber and parallel fiber activity described above ultimately alter Purkinje cell firing. As the sole output of the cerebellar cortex, Purkinje cells are an important target of ethanol's effects (Chu, 1983; Franklin & Gruol, 1987; George & Chu, 1984; Pauli et al., 1995; Phillips & Cragg, 1984; Urrutia & Gruol, 1992; Van Skike et al., 2010). Although LTD at the parallel fiber-Purkinje cell synapse is the representative cellular mechanism underlying motor learning (Ito, 1986), Purkinje cells themselves are an important component of eyeblink conditioning. In Purkinje cell degeneration (*pcd*) mice, which lack Purkinje cells and thereby lack efferent projections to the deep cerebellar nuclei, associative eyeblink conditioning was severely impaired in terms of frequency, amplitude and timing of acquired conditioned

responses (Chen et al., 1996). Notably, acute ethanol exerts a biphasic response on Purkinje cell firing, with low doses administered systemically increasing the spontaneous activity of Purkinje cells and high doses inhibiting spontaneous activity (Chu, 1983). This mirrors the effect of ethanol on eyeblink conditioning in which low doses slightly facilitate (Hernandez & Powell, 1986) and higher doses impair (Hernandez et al., 1986) the acquisition of the conditioned responding. Interestingly, Purkinje cells may not be required for extinction as the *pcd* mice exhibit proper extinction of the conditioned response (Chen et al., 1996).

Another way in which Purkinje cells can directly contribute to cerebellar plasticity is through calcium signaling, which is an integral component of synaptic plasticity (Lamont & Weber, 2012). Climbing fiber activation produces a calcium transient in Purkinje cell dendrites (Knopfel et al., 1991; Ross & Werman, 1987) that is required for induction of parallel fiber LTD (Konnerth et al., 1992). These transients in Purkinje cells are generated by activation of voltage-gated calcium channels (Knopfel et al., 1991; Ross & Werman, 1987), which are affected by application of acute ethanol. For instance, voltage-dependent calcium current amplitude is reduced by application of 50 mM, but not 20 mM, ethanol suggesting that only moderately high ethanol concentrations block Purkinje cell calcium currents and prevent the induction of parallel fiber-LTD (Belmeguenai et al., 2008).

In summary, ethanol can inhibit cerebellar synaptic plasticity through a wide variety of mechanisms (Belmeguenai et al., 2008; Carta et al., 2006; He et al., 2013; Su et al., 2010), but ultimately impairs LTD at the parallel fiber-Purkinje cell synapse, considered to be the cellular correlate of cerebellar learning (Ito, 1986; Jorntell & Hansel, 2006; Valenzuela et al., 2010). Indeed, parallel fiber LTD has been shown to be directly related to eyeblink conditioning (Emi et al., 2013; Yuzaki, 2013), although there are some discrepancies (Schonewille et al., 2011). As

would be expected from the inhibition of parallel fiber LTD by ethanol, ethanol also impairs eyeblink conditioned response acquisition (Hernandez et al., 1986; Hobson, 1966), although a low dose of ethanol may slightly facilitate eyeblink responding (Hernandez & Powell, 1986). Ethanol also impairs extinction of the conditioned response (Hernandez & Powell, 1986; Hernandez et al., 1986), which is mediated by parallel fiber LTP (Jorntell & Hansel, 2006) and climbing fiber inhibition (Medina et al., 2002). Inconveniently, ethanol's effects on the cellular components involved with extinction are the opposite of what the behavior would predict. Ethanol does not affect parallel fiber LTP (Belmeguenai et al., 2008) and climbing fibers are inhibited by ethanol (Carta et al., 2006; He et al., 2013), which should facilitate extinction in light of Medina et al., 2002. Nevertheless, this section demonstrates that ethanol generally inhibits cerebellar learning by inhibiting mechanisms of cerebellar plasticity.

## Amygdala

The amygdala is involved in emotional learning and memory (LaBar & Cabeza, 2006), especially with enhanced reaction and recall of emotionally arousing material. For instance, blood oxygen level dependent activation in the right amygdala is greater for unpleasant words, compared to neutral words (Tabert et al., 2001). Additionally, an increased glucose metabolic rate is positively correlated with long-term recall of emotional, but not neutral, films (Cahill et al., 1996). In animals, the amygdala and its circuits are important for fear conditioning (Kim & Jung, 2006). An elegant series of pharmacological inactivation experiments indicate that the amygdala, while not necessary for innate fear responses, is critically involved in the formation of the learned fear response (Ribeiro et al., 2011).

Compared to contextual fear conditioning which is modulated by hippocampal function (Kim & Fanselow, 1992; Maren & Fanselow, 1997), cued fear conditioning, which modulated by amygdala function (Phillips & LeDoux, 1992; Fanselow & Poulos, 2005; Maren, 2008), is less susceptible to modulations by ethanol. Specifically, 1.0 g/kg and 1.5 g/kg ethanol suppressed cued conditioning by 9% and 17%, compared to 78% and 86% suppression in context conditioning (Melia et al., 1996). There is some evidence that ethanol's effects on fear conditioning may be strain-dependent, and likely genetically influenced. For instance, acute withdrawal 6 hours after a single 4.0 g/kg ethanol exposure increases cued responses in DBA/2J mice, which are withdrawal-sensitive, but does not affect cued responding in C57BL6/6J mice, which are withdrawal-resistant (Tipps et al., 2015). However, acute intoxication has been shown to impact cued fear conditioning in C57BL6/6J mice, suggesting the effects of acute intoxication, as opposed to withdrawal, are not strain- or species- dependent.

Although some studies do not report an ethanol induced impairment in cued fear conditioning (Melia et al., 1996; Weitemier & Ryabinin, 2003) or emotional cue recall (Ray et al., 2012), there is much evidence supporting ethanol induced modulation of emotional memory. Much like memory systems in the cerebellum and recall of explicit long term memories (discussed in the next section), ethanol has bidirectional effects depending on the timing of intoxication relative to learning. Specifically, 0.65 g/kg ethanol administration in humans facilitates recall for material that was viewed before intoxication and decreases recall for material acquired after ethanol consumption. Additionally, there is a greater retrograde facilitation and anterograde impairment for emotional compared to neutral material (Knowles & Duka, 2004), suggesting that the amygdala and its circuits are affected by acute alcohol. This has also been shown in mice with 0.25 g/kg ethanol producing a retrograde enhancement, and 1.0

and 1.5 g/kg ethanol yielding an anterograde impairment of the cued fear response (Gulick & Gould, 2008). Studies in mice suggest that 1.0 and 1.5 g/kg ethanol administration may alter the encoding or acquisition of cued fear conditioning, as ethanol given prior to training disrupts cued conditioning, whereas ethanol intoxication after training or during testing does not impact the cued fear response (Gould, 2003; Gulick & Gould, 2007). The impaired encoding produced by 1.0 g/kg ethanol impairs long-term cued fear memory for at least one week (Gulick & Gould, 2007). Interestingly, studies investigating the effects of acute ethanol exposure on cued fear conditioning in rats are sparser than those conducted in mice, and may have opposing results. This could be due to an effect discovered in a recent study where 1.5 g/kg ethanol administration in Sprague Dawley rats disrupts cued fear acquisition and conditioning, but cued fear deficits were not present when baseline freezing differences were controlled (Broadwater & Spear, 2013).

Although the evidence is somewhat mixed, acute ethanol (Gould, 2003; Gulick & Gould, 2008; Knowles & Duka, 2004) and acute withdrawal (Tipps et al., 2015) appear to impact fear conditioned and emotional memories, which are modulated by the amygdala. Specifically, ethanol produces a retrograde facilitation and anterograde impairment of emotional memories in both humans (Knowles & Duka, 2004) and mice (Gulick & Gould, 2008). These data caution against drinking to alleviate depression, anxiety, or frustration, as ethanol actually facilitates recall of emotional memories acquired before intoxication, rather than relieving one's emotional ailments. Additionally, ethanol appears to exert its short- and long-term anterograde memory impairment through disrupted acquisition or encoding (Gould, 2003; Gulick & Gould, 2007), rather than interfering with retrieval.

## Acute Ethanol and Human Memory

Alcohol produces differential effects on human memory stores that are dependent on many factors including quantity, metabolism, rising or falling phase of intoxication, timing of alcohol relative to learning and recall, and the type of memory considered. For this section, it is assumed that all participants in the studies reviewed have some prior alcohol experience, so the acute effects of alcohol on memory will be defined as those which occur within a single laboratory-controlled drinking episode in moderate alcohol consumers unless otherwise noted. Since alcohol has specific effects on different memory stores, this section will review alcohol's effects on various types of short- and long-term memories.

Working memory is the temporary maintenance of a finite amount of information over a period of several seconds, in such a way that the information can be processed and manipulated. Alcohol dose dependently and selectively impairs certain aspects of working memory. For instance, a moderate dose of alcohol resulting in a BAC of 70 and 90 mg/dL impairs working memory capacity in participants with high, but not low, working memory capacity (Finn et al., 1999). This impairment is likely driven by ethanol's selective impairment on mnemonic strategies needed for encoding and retention rather than a decreased working memory capacity (Saults et al., 2007). Furthermore, alcohol induced memory impairments are dependent on age, such that older participants aged 55-70 years displayed greater working memory impairment at a BAC of 65 mg/dL compared to younger participants aged 25-35 years (Boissoneault et al., 2014).

Additionally, alcohol may impair visual-spatial working memory, particularly on the descending limb of the BAC curve at concentrations near the legal limit. For instance, alcohol impairs performance on a visual-spatial working memory task during the falling phase of BAC

from 90 to 80 mg/dL (Schweizer et al., 2006), however, a different visual-spatial working memory task conducted during the descending limb at an average BAC of approximately 65 mg/dL and did not detect any impairment in visual-spatial working memory (Paulus et al., 2006). A slightly lower mean BAC of 59 mg/dL does not impair spatial working memory, but impairs spatial recognition (Weissenborn & Duka, 2003). Collectively, these data indicate that spatial working memory may be spared by ethanol at mild concentrations, but could be impaired at BACs nearing the legal limit.

As previously alluded to, some working memory impairments are dependent on the phase of ethanol metabolism and are specific to the ascending or descending phases of the BAC curve (Söderlund et al., 2005). This phenomenon is termed acute functional tolerance, which develops within a single drinking session and is characterized by greater impairment on the ascending phase compared to the equivalent BAC on the descending phase (Wallace et al., 2006). In a task of working memory, intoxication at BACs of 68 and 80 mg/dL results in slower reaction time and increased errors during the rising phase of alcohol intoxication. However, the effects of declining BAC on these measures is divergent. Acute functional tolerance develops for reaction time, indicated by a recovery of impairment during declining BACs; whereas tolerance does not develop to working memory errors, which were still increased compared to control participants at BACs of 73 and 64 mg/dL (Grattan-Miscio & Vogel-Sprott, 2005). This pattern of tolerance to reaction time, but not to accuracy exists for several different cognitive functions, including inhibition, information processing, and working memory (as reviewed in Schweizer & Vogel-Sprott, 2008). Curiously, certain types of working memory show ethanol induced impairments only on the descending phase of the BAC curve, but not during the ascending phase, such as the accuracy of visual memory and visual-spatial memory (Schweizer et al., 2006). Importantly,

these data indicate that there are contributors other than BAC levels to alcohol induced memory impairments, as BAC alone does not always predict the level of impairment. Additionally, tolerance is not a global phenomenon; rather tolerance is specific to the type of memory that is being considered.

Situational or environmental factors may be able to regulate intentional control of intoxication states, as certain effects of ethanol on working memory can be modulated by the presence of a reward. Specifically, the alcohol induced deficit in reaction time can be completely countered by a monetary reward, but accuracy is still impaired despite the presence of an incentive (Grattan-Miscio & Vogel-Sprott, 2005). This effect, along with the lack of acute functional tolerance for errors of working memory, indicates that the accuracy of short-term memory may be particularly sensitive to ethanol induced impairments. Given that these effects occur below the current legal limit (64-80 mg/dL), there are safety implications that should be considered for driving at these BAC levels.

Acute alcohol also affects several different aspects of long-term memory, which is comprised of implicit (non-declarative) and explicit (declarative) memories. Implicit memories do not require conscious effort for recall and include procedural memories for performing actions, familiarity, and priming, where prior experience influences current performance. Alcohol consumption differentially affects implicit and explicit memories. For instance, participants learned a task while intoxicated, 60 minutes after consuming either 0.3 or 0.6 g/kg ethanol, and were given tests of explicit memory, measured by free recall, and implicit memory, assessed by backwards-reading and word completion. Both doses of ethanol impaired explicit memory, but not did not impair implicit memory (Lister et al., 1991). Although alcohol administered prior to encoding does not affect the accuracy of implicit memories, it does reduce

awareness of these memories (Duka et al., 2001). The selective deficit of alcohol on explicit memory while sparing implicit memory has strong parallels to rodent data previously reviewed where ethanol selectively impaired allocentric memory while sparing (and perhaps facilitating) egocentric, habit based memory. Specifically, the selective impairment of explicit memory in humans and allocentric memory in rodents would result in an increased reliance on egocentric memory in rodents and intrinsic memory in humans, habitual memory strategies that can occur without conscious recollection. The development of an alcohol use disorder therefore would be the resultant cognitive switch from limbic system function to striatal system function.

Priming tasks are excellent experimental manipulations to test this hypothesis because they measure the transfer from prior memories that are not dependent on conscious recall (Roediger, 1990) and are another way to assess implicit memory. Alcohol-related implicit priming cues increase alcohol consumption in a laboratory setting (Roehrich & Goldman, 1995) exactly as would be predicted. However, implicit alcohol expectancies are not changed by BACs of 75 to 80 mg/dL as measured with the Implicit Associations Test in current drinkers (Pedersen et al., 2011). In contrast, at a BAC of 40 mg/dL, risky drinkers showed increased response time toward positive alcohol outcomes compared to negative outcomes (Palfai & Ostafin, 2003). These implicit cognitions regarding alcohol expectancies are important contributors to drinking behavior, as implicit expectations predict alcohol consumption along with explicit expectations (Stacy, 1997). It follows that heavy drinkers have stronger positive implicit associations for alcohol expectancies than lighter drinkers (Palfai & Ostafin, 2003; Pedersen et al., 2011; Wiers et al., 2002). In summary, it appears that alcohol intoxication does not directly impair implicit memory, although it can reduce awareness of these memories. Additionally, acute alcohol

intoxication only affects implicit alcohol expectancies in risky drinkers, but does not change implicit expectancies in moderate alcohol consumers.

Explicit or declarative memories are memories that can be consciously recalled, and fall into two main categories: episodic and semantic and would expected to be impaired by alcohol. Episodic memory is a type of long-term memory for specific events and the temporal-spatial relationships among different events, while semantic memory is used for language (Tulving, 1972). The difference between these two types of memory stores is difficult to distinguish in a laboratory setting, leading some to argue against a functional separation of the episodic and semantic memory systems (McKoon & Ratcliff, 1979); therefore, explicit memory will be considered as a whole in this section.

Perhaps the most obvious impairment of explicit memory comes from ethanol induced blackouts. These blackouts can be either fragmentary, where only certain memories are lost and may be retrievable with sufficient cuing, or en bloc, in which ethanol induced amnesia for the intoxication period is permanent (Lee et al., 2009). En bloc blackouts are less common than fragmentary blackouts, but the rate of occurrence for both types of blackouts increases with increasing BAC (Hartzler & Fromme, 2003). However, fragmentary blackouts can occur with estimated BACs below the legal limit (Hartzler & Fromme, 2003). Additionally, some individuals, without sober memory deficits, may be more vulnerable to alcohol induced blackouts: These individuals report blackouts at BACs that do not induce blackouts in others at the same BAC level (Wetherill & Fromme, 2011). Furthermore, alcohol has differential effects on blood oxygenation level-dependent (BOLD) activity during contextual recall in those with and without history of fragmentary blackouts, despite similar BOLD activation during recall when sober (Wetherill et al., 2012). Not only can alcohol prevent encoding for remembering

what has happened in the immediate past, it can also impair memory for future tasks, termed prospective memory. There are several different distinctions within this memory category, including time-based (remembering something to be done at a specific time) versus event-based (remembering to do the task itself) and regularly occurring tasks (medications) versus irregular occurrences (pick up the dry cleaning). Acute alcohol intoxication impairs all types of prospective memory (Leitz et al., 2009).

Alcohol differentially impacts explicit memory based on whether the alcohol is consumed before or after learning. For instance, when participants were intoxicated at a BAC of 70 mg/dL during an incidental learning task, free recall was impaired; however, this deficit could be countered by providing cues (Birnbaum et al., 1978). Additionally, free recall after intoxicated word learning was shown to be significantly impaired by BACs of 54 mg/dL, but not 17 mg/dL (Lister et al., 1991). In contrast, when free recall and paired-associate lists were learned sober, intoxicated free recall after a one week delay was similar compared to people who both learned and recalled sober (Birnbaum et al., 1978). Similarly, consumption of 0.65 g/kg alcohol facilitates emotional memory for images seen before intoxication, and impairs memory for images presented after intoxication (Knowles & Duka, 2004). These data indicate that moderate intoxication during encoding negatively impacts recall, whereas intoxication at the time of retrieval is not impaired and may even be facilitated by ethanol.

Additionally, ethanol has been shown to enhance other aspects of episodic memory involving recognition, as ethanol intoxication yielding a BAC of 80 mg/dL can retroactively enhance memory for recent information acquired when given immediately after sober learning (Parker et al., 1980), and this effect can occur with BACs as low as 34 mg/dL (Parker et al., 1981). Furthermore, BACs of 80 mg/dL were associated with enhanced free- and cued- word

recall 24 hours after an incidental learning task (Parker et al., 1980). This retroactive memory enhancement has been attributed to enhanced trace consolidation (Parker et al., 1981) and reduced acquisition of interfering memories (Hewitt et al., 1996; Mueller et al., 1983). Collectively, these studies show that ethanol does not produce a global memory impairment, and can in fact facilitate some aspects of long-term memory.

At a neurological level, impaired encoding is associated with reduced activity in various brain regions based on the type of information being encoded: Inactivation of the left inferior frontal gyrus for nonverbal information, reduced right middle frontal gyrus activity for objects, reduced activity of the right inferior frontal gyrus for face-name pairs, and reduced parahippocampal and fusiform gyri activity for objects were associated with impaired memory performance during intoxication (Söderlund et al., 2007). However, alcohol does not impair verbal encoding and memory, which corresponds to similar activation in both intoxicated and control participants of the left prefrontal regions during encoding (Söderlund et al., 2007). Impairment of other brain regions have also been implicated in the negative effects of acute alcohol on memory performance. In fact, alcohol intoxication with a mean peak BAC of 103 mg/dL has been compared to memory deficits seen in patients with prefrontal lobe damage due to the alcohol induced impairments of executive functioning, including impaired working and perceptual memory (Peterson et al., 1990). In sum, alcohol alters brain function (Oscar-Berman & Marinković, 2007), which can manifest as impairments in learning and memory (Peterson et al., 1990; Söderlund et al., 2007).

Collectively, these studies on ethanol-induced memory impairments show that acute ethanol does not produce a global memory impairment (see table 2 for summary). Regarding explicit long-term memory, alcohol intoxication impairs prospective memory (Leitz et al., 2009)

and memory encoding (Birnbaum et al., 1978; Lister et al., 1991), but facilitates retrieval (Parker et al., 1980) and does not affect long-term implicit memories (Lister et al., 1991). The differential effects on encoding compared to retrieval highlight that the timing of ethanol exposure relative to learning and recall is imperative in determining its effects. Similarly, various types of short-term working memory are differentially impaired by the different phases of ethanol metabolism (Schweizer et al., 2006), indicating that BAC alone does not predict alcohol's effects. As outlined previously and supported in the reviewed human imaging studies, acute alcohol intoxication alters functioning of the limbic circuitry centered on the hippocampus and prefrontal lobs, particularly in the right hemisphere(Oscar-Berman & Marinković, 2007), which corresponds to impaired memory performance (Peterson et al., 1990; Söderlund et al., 2007), and likely facilitates behavioral control of the sensorimotor circuitry. Additionally, several impairments in both short- and long- term memory occur below the current legal limit in the United States of 80 mg/dL (see table 2), indicating that this BAC should not necessarily be considered a safe level of intoxication.

## Conclusions and Future Directions

Acute alcohol exposure alters multiple memory systems and likely produces these effects by altering neural function through a variety of mechanisms that are dependent on dose, brain region, task demands, and timing of ethanol exposure relative to training and testing (see Tables 1 and 2 for summary). Additionally, individual sensitivities to the intoxicating effects of ethanol are dependent on genetics, pharmacokinetics, pharmacodynamics, tolerance, and social factors, among others.

The hippocampus has received much attention due to its particular vulnerability to ethanol-induced impairments of behavior and neural function and its importance in learning and memory. With the exception of certain types of challenging spatial working memory tasks, ethanol produces dose dependent impairments in hippocampal based learning and memory tasks regardless of the motivational, behavioral, or temporal nature of the experimental procedure. In addition, it has been determined that there are at least two mechanisms by which ethanol produces these impairments: 1. Through altering medial septal acetylcholine and GABAergic projections into the hippocampus and 2. By increasing allopregnanolone levels directly in the hippocampus.

Alcohol was known to impair cerebellar functioning long before the cognitive functions of the cerebellum were appreciated and received extensive study. Cerebellar synaptic plasticity is impaired by alcohol through a wide variety of mechanisms, including inhibiting LTD at the parallel fiber-Purkinje cell synapse, which is considered to be the cellular correlate of cerebellar learning (Ito, 1986; Jorntell & Hansel, 2006; He et al., 2013; Su et al., 2010). Mirroring this effect, moderate to high doses of ethanol also impair the acquisition of conditioned eyeblink responding (Hernandez et al., 1986; Hobson, 1966). Together, the data indicate that ethanol likely impairs cerebellar learning by inhibiting mechanisms of cerebellar plasticity.

Although discrepancies have been found regarding amygdala dependent fear conditioning, there is some evidence in both animal models and humans that ethanol produces a retrograde facilitation and anterograde impairment of fear conditioned and emotional memories (Gulick & Gould 2008; Knowles & Duka, 2004). This bidirectional effect is similar to alcohol's effects on explicit long-term memory: intoxication impairs prospective memory (Leitz et al.,

2009) and memory encoding (Birnbaum et al., 1978; Lister et al., 1991), but facilitates retrieval (Parker et al., 1980). Therefore, alcohol does not produce global memory impairments.

While much is currently known about the effects of acute alcohol on learning and memory, several issues remain unknown and are in need of additional investigation. Fortunately, research has progressed to the point where specific studies can be proposed and predicted results can be hypothesized. For example, additional studies are needed that directly investigate the effect of ethanol on cognition while neural activity is being concomitantly recorded. Although these studies are technologically difficult and time consuming, the marrying of ongoing brain activity with behavior is needed to more fully understand how alcohol impairs cognition.

Specifically, it is well known that acute alcohol administration produces impairments in hippocampal-dependent spatial memory tasks without producing impairments in caudate dependent non-spatial tasks. In addition, recent research has shown that spatial memory in adolescent and adult animals, compared to aged animals, is less impaired by acute alcohol exposure. Based on these previous findings, if animals of different ages (adolescent, adult and aged) are trained on a task that can be performed using either spatial (hippocampal dependent) or non spatial (caudate dependent) strategies while the neural activity of hippocampal and caudate neurons are recorded, it can be predicted that acute alcohol exposure will produce significantly greater alterations in the neural activity of hippocampal neurons compared to caudate neurons and the greater alterations will significantly correlate with animal age. In more general terms, the research field has progressed to the point of predicting results based on brain region, age and task.

Secondly, almost no informative genetic work has been accomplished on ethanol's ability to impair learning and memory. With the development of consomic and recombinant inbred

mouse strains such as the BxD strains, rapid understanding of candidate genes underlying ethanol's ability to alter cognition could occur. Third, it is important to determine the parameters of when acute alcohol produces greater, or less, cognitive impairments in adolescents compared to adults. The potential government policy issues related to this issue is of great importance, but currently little agreement exists in the field and work should more systematically address this issue. Fourth, advanced behavioral studies need to be conducted to more fully explore if acute alcohol exposure facilitates striatal-based, habit learning, at the expense of other types of learning, and assess the dynamics and mechanisms of such shifts from goal-directed to habit-based behaviors (Gremel et al., 2016). Of particular interest is whether the propensity to develop habit learning is genetically correlated with family history for alcohol use disorder (or in rodent selected lines, genetic predisposition for high voluntary alcohol drinking), and the extent to which facilitated habit formation depends on the history of alcohol use. Finally, virtual techniques (e.g., virtual Morris water maze) exist for use with human subjects that are similar to techniques used in animal models. The use of these virtual techniques coupled with alcohol exposure will greatly bridge the animal and human work and allow for the field to become truly translational in nature.

Alcohol is among the most used and abused drug in the world and has a profound impact on learning and memory. Given the importance of cognition in the human life, better understanding of how alcohol impacts learning and memory throughout the lifespan is a critical and important research area. Our hope is that be telling the story of where the field has been we will facilitate the development of exciting research strategies to fully understand the complex interaction of alcohol and cognition.

## References

Acheson, S. K., Bearison, C., Risher M. L., Abdelwahab, S. H., Wilson, W. A. & Swartzwelder, H. S. (2013). Effects of acute or chronic ethanol exposure during adolescence on behavioral inhibition and efficiency in a modified water maze task. *PLOS One, 8,* 1-15.

Alvarado, M.C. & Rudy, J.W. (1995). Rats with damage to the hippocampus-formation are impaired on the transverse-patterning problem but not on the elemental discriminations. Behavioral Neuroscience, 109, 204-211.

Baddeley, A.D. (1983). Working memory. Phil Trans R Soc Lond B, 302, 311-324.

Balleine, B.W., Delgado, M.R. & Hikosaka, O. (2007). The role of the dorsal striatum in reward and decision making. The Journal of Neuroscience, 27, 8131-8165.

Balleine, B.W. & Dickinson, A. (1998). Goal-directed instrumental action: contingency and incentive learning and their cortical substrates. Neuropharmacology, 37, 407-419.

Barbaccia, M. L., Affricano, D., Trabucchi, M., Purdy, R. H., Colombo, G., Agabio, R. & Gessa, G. L. (1999). Ethanol markedly increases "GABAergic" neurosteroids in alcohol preferring rats. *Eur J Pharmacol, 384,* R1-R2.

Bechara, A., Tranel, D., Damasio, H. Adolphs, R. Rockland, C. & Damasio, A.R. (1995). Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. Science, 269, 1115-1118.

Belmeguenai, A., Botta, P., Weber, J. T., Carta, M., De Ruiter, M., De Zeeuw, C. I., . . . Hansel, C. (2008). Alcohol Impairs Long-Term Depression at the Cerebellar Parallel Fiber-Purkinje Cell Synapse. *J Neurophysiol, 100*(6), 3167-3174. doi: 10.1152/jn.90384.2008

Berry, R. B., Chandra, D., Diaz-Granados, J. L., Homanics, G. E. & Matthews, D. B. (2009). Investigation of ethanol-induced impairment of spatial memory in gamma2 heterozygous knockout mice. *Neurosci Lett, 455*(2), 84-7.

Berry, R. B. & Matthews, D. B. (2004). Acute ethanol administration selectively impairs spatial memory in C57BL/6J Mice. *Alcohol, 32,* 9-18.

Berry, R. B., Werner, D. F., Wang, X., Jablonski, M. M., Homanics, G. E., Mittleman, G. & Matthews, D. B. (2008). Mice with targeted genetic reduction of GABA(A) receptor alpha1 subunits display performance differences in Morris water maze tasks. *Neurobiol Learn Mem, 90*(3), 580-3.

Berry, S. D. & Hoffmann, L. C. (2011). Hippocampal theta-dependent eyeblink classical conditioning: Coordination of a distributed learning system. *Neurobiol Learn Mem,* 95, 185-189.

Best, P. J. & White, A. M. (1999). Placing hippocampal single-unit studies in a historical context. *Hippocampus, 9,* 346-351.

Best, P. J., White, A. M. & Minai, A. (2001). Spatial processing in the brain: The activity of hippcocampal place cells. *Annu Rev Neurosci, 24,* 459-486.

Birnbaum, I. M., Parker, E. S., Hartley, J. T., & Noble, E. P. (1978). Alcohol and memory: Retrieval processes. *J Verb Learn Verb Be, 17*(3), 325-335. doi: http://dx.doi.org/10.1016/S0022-5371(78)90210-4

Black, J. E., Isaacs, K. R., Anderson, B. J., Alcantara, A. A., & Greenough, W. T. (1990). Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. *Proc Natl Acad Sci U S A, 87*(14), 5568-5572.

Blitzer, R. D., Gil, O. & Landau, E. M. (1990). Long-term potentiation in rat hippocampus is inhibited by low concentrations of ethanol. *Brain Res, 537,* 203-208.

Boening, J. A. L. (2001). Neurobiology of addiction memory. *J Neural Transm, 108,* 755-765.

Boissoneault, J., Sklar, A., Prather, R., & Nixon, S. J. (2014). Acute effects of moderate alcohol on psychomotor, set shifting, and working memory function in older and younger social drinkers. *J Stud Alcohol Drugs, 75*(5), 870-879.

Broadwater, M., & Spear, L. P. (2013). Age differences in fear retention and extinction in male Sprague-Dawley rats: Effects of ethanol challenge during conditioning. *Behav Brain Res, 252,* 377-387. doi: http://dx.doi.org/10.1016/j.bbr.2013.06.029

Brown, K. L., Calizo, L. H., Goodlett, C. R., & Stanton, M. E. (2007). Neonatal alcohol exposure impairs acquisition of eyeblink conditioned responses during discrimination learning and reversal in weanling rats. *Dev Psychobiol, 49*(3), 243-257. doi: 10.1002/dev.20178

Buckner, Randy L. (2013). The Cerebellum and Cognitive Function: 25 Years of Insight from Anatomy and Neuroimaging. *Neuron, 80*(3), 807-815. doi: http://dx.doi.org/10.1016/j.neuron.2013.10.044

Cahill, L., Haier, R. J., Fallon, J., Alkire, M. T., Tang, C., Keator, D., . . . McGaugh, J. L. (1996). Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Proc Natl Acad Sci U S A, 93*(15), 8016-8021.

Cai, Q., Wu, J., Cai, Q., Chen, E. Z., & Jiang, Z. Y. (2015). Association between Glu504Lys Polymorphism of ALDH2 Gene and Cancer Risk: A Meta-Analysis. *PLoS One, 10*(2), e0117173. doi: 10.1371/journal.pone.0117173

Carta, M., Mameli, M., & Valenzuela, C. F. (2006). Alcohol potently modulates climbing fiber-->Purkinje neuron synapses: role of metabotropic glutamate receptors. *J Neurosci, 26*(7), 1906-1912. doi: 10.1523/JNEUROSCI.4430-05.2006

Carta, I., Chen, C.H. Schott, A., Dorizan, S. & Khodakhah, K. (2019). Cerebellar modulation of the reward circuitry and social behavior. *Science,* 363(6424).

Cavada. C., Compañy, T., Tejedor, J., Cruz-Rizzolo, R.J., and Reinoso-Suárez, F. (2000). Tthe anatomical connections of the macaque monkey orbitofrontal cortex. A review. Cereb Cortex, 10, 220-242.

Chandrasekar, R. (2013). Alcohol and NMDA receptor: current research and future direction. *Front Mol Neurosci, 6,* 1-27.

Chen, C., & Thompson, R. F. (1995). Temporal specificity of long-term depression in parallel fiber--Purkinje synapses in rat cerebellar slice. *Learn Mem, 2*(3-4), 185-198.

Chen, L., Bao, S., Lockard, J. M., Kim, J. K., & Thompson, R. F. (1996). Impaired classical eyeblink conditioning in cerebellar-lesioned and Purkinje cell degeneration (pcd) mutant mice. *J Neurosci, 16*(8), 2829-2838.

Cheng, D.T., Disterhoft, J.F., Power, J.M., Ellis, D.A. & Desmond, J.E. (2008). Neural substrates underlying human delay and trace eyeblink conditioning. PNAS, 105, 8108-8113.

Cheng, D.T., Jacobson, S.W., Jacobson, J.L., Molteno, C.D., Stanton, M.E. & Desmond, J.E. (2015). Eyeblink classical conditioning in alcoholism and fetal alcohol spectrum disorders. *Front Psychi,* 155.

Chu, N. S. (1983). Effects of ethanol on rat cerebellar Purkinje cells. *Int J Neurosci, 21*(3-4), 265-277.

Chin, V.S., Van Skike, C.E. & Matthews, D.B. 2010). Effects of ethanol on hippocampal function during adolescence: A look at the past and thoughts on the future. *Alcohol,* 44, 3-14.

Cook, J. B., Nelli, S. M., Neighbors, M. R., Morrow, D. H., O'Buckley, T. K., Maldonado-Devincci, A. M. & Morrow, A. L. (2014). Ethanol alters local cellular levels of (3a,5a)-3-Hydroxypregnan-20-one (3a,5a-THP) independent of the adrenals in subcortical brain regions. *Neuropsychopharmacol, 39,* 1978-1987.

Cook, J. G., Dumitru, A. M., O'Buckley, T. K. & Morrow, A. L. (2014). Ethanol administration produces divergent changes in GABAergic neuroactive steroid immunohistochemistry in the rat brain. *Alcoholism Clin Exp Res, 38,* 90-99.

Corbit, L.H. & Balleine, B.W. (2003). The role of prelimbic cortex in instrumental conditioning. Behavioral Brain Research, 146, 145-157.

Corbit, L.H. & Janak, P.H. (2007). Ethanol-associated cues produce general Pavlovian-instrumental transfer. *Alcoholism Clin Exp Res,* 31, 766-774.

Corbit, L.H. & Janak, P.H. (2007). Inactivation of the lateral but not medial dorsal striatum eliminates the excitatory impact of Pavlovian stimuli on instrumental responding. The Journal of Neuroscience, 27, 13977-13981.

Corbit, L.H. Janak, P.H., Balleine, B.W. (2007). General and outcome-specific forms of Pavlovian-instrumental transfer: the effect of shifts in motivational state and inactivation of the ventral tegmental area. European J Neuro, 26, 3141-3149.

Corbit, L.H. & Janak, P.H. (2010). Posterior dorsomedial striatum is critical for both selective instrumental and Pavlovian reward learning. European J Neuro, 31, 1312-1321.

Corbit, L.H., Nie, H. & Janak, P.H. (2012). Habitual alcohol seeking: Time course and the contribution of subregions of the dorsal striatum. Biol Psychiatry, 723, 389-395.

Corbit, L.H. & Janak, P.H. (2016). Habitual alcohol seeking: neural bases and possible relations to alcohol use disorders. Alcoholism Clin Exp Res, 40, 1380-1389.

Corkin, Suzanne. (2002). What's new with the amnesic patient H.M.? Nature Reviews, 3, 153-160.

Cox, T. (1970). The effects of caffeine, alcohol, and previous exposure to the test situation on spontaneous alternation. *Psychopharmacologia, 17*, 83-88.

Cushman, J. D., Moore, M. D., Jacobs, N. S., Olsen, R. W., & Fanselow, M. S. (2011). Behavioral pharmacogenetic analysis on the role of the alpha4 GABA(A) receptor subunit in the ethanol-mediated impairment of hippocampus-dependent contextual learning. *Alcohol Clin Exp Res*, *35*(11), 1948-1959. doi: 10.1111/j.1530-0277.2011.01546.x

Daum, I., Schugens, M. M., Ackermann, H., Lutzenberger, W., Dichgans, J., & Birbaumer, N. (1993). Classical conditioning after cerebellar lesions in humans. *Behav Neurosci*, *107*(5), 748-756.

DePoy, L., Daut, R., Brigman, J. L., MacPherson, K., Crowley, N., Gunduz-Cinar, O., Pickens, C. L., Cinar, R., Saksida, L. M., Kunos, G., Lovinger, D. M., Bussey, T. J., Camp, M. C., … Holmes, A. (2013). Chronic alcohol produces neuroadaptations to prime dorsal striatal learning. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(36), 14783-8.

Devenport, L., Stidham, J., & Hale, R. (1989). Ethanol and spatial localization. *Behav Neurosci*, *103*, 1259-1266.

Devenport, L. D. & Cater, N. (1986). Ethanol blockade of context change effects. *Behav Neural Biol*, 45, 135-142.

Devenport, L. D. & Hale, R.L. (1989). Contributions of hippocampus and neocortex to the expression of ethanol effects. *Psychopharmacology*, *99*, 337-344.

Devenport, L. D. & Merriman, V. J. (1983). Ethanol and behavioral variability in the radial-arm maze. *Psychopharmacology*, 79, 21-24.

Devenport, L. D. (1984). Extinction-induced spatial dispersion in the radial arm maze: Arrest by ethanol. *Behav Neurosci*, *98*, 979-985.

Devenport, L. D., Merriman, V. J. & Devenport, J. A. (1983). Effects of ethanol on enforced spatial variability in the 8-arm radial arm maze. *Pharmacol Biochem Be*, *18*, 55-59.

Duka, T., Weissenborn, R., & Dienes, Z. (2001). State-dependent effects of alcohol on recollective experience, familiarity and awareness of memories. *Psychopharmacology (Berl), 153*(3), 295-306. doi: 10.1007/s002130000564

Emi, K., Kakegawa, W., Miura, E., Ito-Ishida, A., Kohda, K., & Yuzaki, M. (2013). Reevaluation of the role of parallel fiber synapses in delay eyeblink conditioning in mice using Cbln1 as a tool. *Front Neural Circuits, 7*, 180. doi: 10.3389/fncir.2013.00180

Escher, T. & Mittleman, G. (2004). Effects of ethanol and GABAB drugs on working memory in C56BL/6J and DBA/2J mice. *Psychopharmacology (Berl), 176*(2), 166-74.

Everitt, B.J. & Robbins, T.W. (2005). Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nature Neuroscience, 8, 1481-1490.

Everitt, B.J. & Robbins, T.W. (2016). Drug addiction: Updating actions to habits to compulsions ten years on. Annu Rev Psychol, 67, 23-50.

Fanselow, M.S. & Dong, H.W. (2010). Are the dorsal and vetral hippocampus functionally distinct structures? *Neuron*, 14, 1-25.

Fanselow, M. S. & Poulos, A. M. (2005). The neuroscience of mammalian associate learning. *Annu Rev Psychol, 56*, 207-234.

Finn, P. R., Justus, A., Mazas, C., & Steinmetz, J. E. (1999). Working memory, executive processes and the effects of alcohol on Go/No-Go learning: testing a model of behavioral regulation and impulsivity. *Psychopharmacology (Berl), 146*(4), 465-472.

Ford, M.M., Nickel, J.D., Kaufman, M.N. & Finn, D.A. (2015). Null Mutation of 5α-Reductase type 1 gene alters ethanol consumption patterns in a sex-dependent manner. Behavior Genetics, 45, 341-353.

Franklin, C. L., & Gruol, D. L. (1987). Acute ethanol alters the firing pattern and glutamate response of cerebellar Purkinje neurons in culture. *Brain Res, 416*(2), 205-218.

Franks, C. M. (1963). The Apparent Failure of Ethyl Alcohol to Inhibit the Formation of Conditioned Eyeblink Responses in Man. *Psychopharmacologia, 4*, 433-440.

Gawel, K., Labuz, K., Gibula-Bruzda, E., Jenda, M., Marszalek-Grabska, M., Filarowska, J., Silberring, J. & Kotlinska, J.H. (2016). Cholinesterase inhibitors, donepezil and rivastigmine, attenuate spatial memory and cognitive flexibility impairments induced by acute ethanol in the Barnes maze task in rats. *Naunyn-Schmiedeberg's Arch Pharm*, 389, 1059-1071.

George, F., & Chu, N. S. (1984). Effects of ethanol on Purkinje cells recorded from cerebellar slices. *Alcohol, 1*(5), 353-358.

Gibson, W. E. (1985). Effects of alcohol on radial maze performance in rats. *Physiol Behav, 35*(6): 1003-1005.

Gilman, J.M., Smith, A.R., Ramchandani, V.A., Momenan, R. & Hommer, D.W. (2012). The effect of intravenous alcohol on the neural correlates of risky decision making in healthy social drinkers. *Addict Biol*., 17, 465-478.

Givens, B. & McMahon, K. (1997). Effects of ethanol on nonspatial working memory and attention. *Behav Neurosci, 111*, 275-282.

Givens, B. (1995). Low doses of ethanol impair spatial working memory and reduce hippocampal theta activity. *Alcohol Clin Exp Res, 19*, 763-767.

Givens, B., Williams, J. M. & Gill, T. M. (2000). Septohippocampal pathway as a site for the memory-impairing effects of ethanol. *Hippocampus, 10*, 111-121.

Givens, B. S. & Breese, G. R. (1990). Electrophysiological evidence that ethanol alters function of medial septal area without affecting lateral septal function. *J Pharmacol Exp Ther, 253*, 95-103.

Gold, P.E. (2003). Acetylcholine modulation of neural systems involved in learning and memory. Neurobiol Learn Mem, 80, 194-210.

Gould, T. J. (2003). Ethanol disrupts fear conditioning in C57BL/6 mice. *J Psychopharmacol, 17*(1), 77-81.

Grattan-Miscio, K. E., & Vogel-Sprott, M. (2005). Effects of alcohol and performance incentives on immediate working memory. *Psychopharmacology (Berl), 181*(1), 188-196. doi: 10.1007/s00213-005-2226-2

Green, J. T. (2003). Using eyeblink classical conditioning as a test of the functional consequences of exposure of the developing cerebellum to alcohol. *Integr Physiol Behav Sci, 38*(1), 45-64.

Green, J. T., Rogers, R. F., Goodlett, C. R., & Steinmetz, J. E. (2000). Impairment in eyeblink classical conditioning in adult rats exposed to ethanol as neonates. *Alcohol Clin Exp Res, 24*(4), 438-447.

Gremel, C.M., Chancey, J.H., Atwood, B.K., Luo, G., Neve, R., Ramakrishnan, C., Deisseroth, K., Lovinger, D.M. & Costa, R.M. (2016) Endocannabinoid modulation of orbitostriatal circuits gates habit formation. Neuron, 90, 1312-1324.

Gremel, C.M. & Lovinger, D.M. (2017). Associative and sensorimotor cortico-basal ganglia circuit roles in effects of abused drugs. Genes, Brain and Behavior, 16, 71-85

Grobin, A. C., Matthews, D. B., Devaud, L. L. & Morrow, A. L. (1998). The role of GABAa receptors in the acute and chronic effects of ethanol. *Psychopharmacology, 139*, 2-19.

Gross, C. G. & Black, P. (1968). Hippocampal lesions: Effects on memory in rats. *Psychon Sci, 12*, 165-166.

Gu, J. Y., & Li, L. W. (2014). ALDH2 Glu504Lys polymorphism and susceptibility to coronary artery disease and myocardial infarction in East Asians: a meta-analysis. *Arch Med Res, 45*(1), 76-83. doi: 10.1016/j.arcmed.2013.10.002

Gulick, D. & Gould, T. (2008). Interactive effects of ethanol and nicotine on learning in C57BL/6J mice depend on both dose and duration of treatment. *Psychopharmacology (Berl), 196*(3), 483-495. doi: 10.1007/s00213-007-0982-x

Gulick, D. & Gould, T. J. (2007). Acute ethanol has biphasic effects on short- and long-term memory in both foreground and background contextual fear conditioning in C57BL/6 mice. *Alcohol Clin Exp Res, 31*(9), 1528-1537. doi: 10.1111/j.1530-0277.2007.00458.x

Harrison, N. L., Majewska, M. D., Harrington, J. W., & Barker, J. L. (1987). Structure-activity relationships for steriod interaction with the gamma-aminobutyric acidA receptor complex. *J Pharmacol Exp Ther, 241*(1): 346-53.

Hartzler, B. & Fromme, K. (2003). Fragmentary and en bloc blackouts: similarity and distinction among episodes of alcohol-induced memory loss. *J Stud Alcohol, 64*(4), 547-550.

He, Q., Titley, H., Grasselli, G., Piochon, C., & Hansel, C. (2013). Ethanol affects NMDA receptor signaling at climbing fiber-Purkinje cell synapses in mice and impairs cerebellar LTD. *J Neurophysiol, 109*(5), 1333-1342. doi: 10.1152/jn.00350.2012

Hefner, K. & Holmes, A. (2007). An investigation of the behavioral actions of ethanol across adolescence in mice. *Psychopharmacology, 191*(2), 311-322.

Henn, C. Loffelholz, K. & Klein J. (1998). Stimulatory and inhibitory effects of ethanol on hippocampal acetylcholine release. *Naunyn Schmiedebergs, Arch Pharm*, 357, 640-647.

Hernandez, L. L., & Powell, D. A. (1986). Ethanol enhancement of Pavlovian conditioning: comparison with instrumental conditioning. *Psychopharmacology (Berl), 88*(1), 75-81.

Hernandez, L. L., Valentine, J. D., & Powell, D. A. (1986). Ethanol enhancement of pavlovian conditioning. *Behav Neurosci, 100*(4), 494-503.

Hewitt, G. P., Holder, M., & Laird, J. (1996). Retrograde enhancement of human kinesthetic memory by alcohol: consolidation or protection against interference? *Neurobiol Learn Mem, 65*(3), 269-277. doi: 10.1006/nlme.1996.0032

Hicklin, T. R., Wu, P. H., Radcliffe, R. A., Freund, R. K., Goebel-Goody, S. M., Correa, P. R., . . . Browning, M. D. (2011). Alcohol inhibition of the NMDA receptor function, long-term potentiation, and fear learning requires striatal-enriched protein tyrosine phosphatase. *Proc Natl Acad Sci U S A, 108*(16), 6650-6655. doi: 10.1073/pnas.1017856108

Hobson, G. N. (1966). Ethanol inhibition of formation of conditioned eyeblink responses in man. *Psychopharmacologia, 9*(2), 93-100.

Hoffmann, S.E. & Matthews, D.B. (2001). Ethanol-induced impairments in spatial working memory are not due to deficits in learning. *Alcohol Clin Exp Res, 25*, 856-861.

Hunt, P.S. & Barnet, R.C. (2016). Adolescent and adult rats differ in the amnesic effects of acute ethanol in two hippocampus-dependent tasks: Trace and contextual fear conditioning. *Behav Brain Res, 298, 78-87.*

Hunt, P. S., Levillain, M. E., Spector, B. M., & Kostelnik, L. A. (2009). Post-training ethanol disrupts trace conditioned fear in rats: Effects of timing of ethanol, dose and trace interval duration. *Neurobiol Learn Mem, 91*, 73-80.

Ito, M. (1986). Long-term depression as a memory process in the cerebellum. *Neuroscience Research, 3*(6), 531-539. doi: 10.1016/0168-0102(86)90052-0

Ito, M. (1989). Long-term depression. *Annu Rev Neurosci, 12*, 85-102. doi: 10.1146/annurev.ne.12.030189.000505

Ito, M., & Kano, M. (1982). Long-lasting depression of parallel fiber-Purkinje cell transmission induced by conjunctive stimulation of parallel fibers and climbing fibers in the cerebellar cortex. *Neurosci Lett, 33*(3), 253-258.

Izumi, Y., Murayama, K., Tokuda, K., Krishnan, K., Covey, D.F. & Zorumski, C.F. (2007). GABAergic neurosteroids mediate the effects of ethanol on long-term potentiation in rat hippocampal slices. *Eur J Neurosci, 26*, 1881-1888.

Jacobson, S. W., Stanton, M. E., Dodge, N. C., Pienaar, M., Fuller, D. S., Molteno, C. D., . . . Jacobson, J. L. (2011). Impaired delay and trace eyeblink conditioning in school-age children with fetal alcohol syndrome. *Alcohol Clin Exp Res, 35*(2), 250-264. doi: 10.1111/j.1530-0277.2010.01341.x

Jamal, M., Ameno, K., Miki, T., Tanaka, N., Ono, J., Shirakami, G., . . . Kinoshita, H. (2012). High ethanol and acetaldehyde impair spatial memory in mouse models: Opposite effects of aldehyde dehydrogenase 2 and apolipoprotein E on memory. *Pharmacol Biochem Be, 101*(3), 443-449. doi: http://dx.doi.org/10.1016/j.pbb.2012.02.006

Jarrard, L. E. (1993). On the role of the hippocampus in learning and memory in the rat. *Behav Neural Biol, 60*, 9-26.

Jarrard, L. E., Okaichi, H., Steward, W., & Goldschmidt, R.B. (1984). On the role of hippocampal connections in the performance of place and cue tasks: Comparisons with damage to hippocampus. *Behav Neurosci, 98*, 946-954.

Jedema, H.P., Carter, M.D., Dugan, B.P., Gurnsey, K., Olsen, A.S & Bradberry, C.W. (2011). The acute impact of ethanol on cognitive performance in Rhesus Macaques. Cerebral Cortex, 21, 1783-1791.

Jorntell, H., & Hansel, C. (2006). Synaptic memories upside down: bidirectional plasticity at cerebellar parallel fiber-Purkinje cell synapses. *Neuron, 52*(2), 227-238. doi: 10.1016/j.neuron.2006.09.032

Kalmbach, B. E., Davis, T., Ohyama, T., Riusech, F., Nores, W. L., & Mauk, M. D. (2010). Cerebellar cortex contributions to the expression and timing of conditioned eyelid responses. *J Neurophysiol, 103*(4), 2039-2049. doi: 10.1152/jn.00033.2010

Kim, J. J., & Jung, M. W. (2006). Neural circuits and mechanisms involved in Pavlovian fear conditioning: A critical review. *Neurosci Biobehav Rev, 30*(2), 188-202. doi: 10.1016/j.neubiorev.2005.06.005

Kim, J. J. & Fanselow, M. S. (1992). Modality-specific retrograde amnesia of fear. *Science, 256,* 675-677.

Kleim, J. A., Lussnig, E., Schwarz, E. R., Comery, T. A., & Greenough, W. T. (1996). Synaptogenesis and FOS expressionin the motor cortex of the adult rat after motor skill learning. *J Neurosci, 16*(14), 4529-4535.

Kleim, J. A., Swain, R. A., Armstrong, K. A., Napper, R. M. A., Jones, T. A., & Greenough, W. T. (1998). Selective synaptic plasticity within the cerebellar cortex following complex motor skill learning. *Neurobiol Learn Mem, 69*(3), 274-289. doi: DOI 10.1006/nlme.1998.3827

Klemm, W. R., Mallari, C. G., Dreyfus, L. R., Fiske, J. C., Forney, E., & Mikeska, J. A. (1976). Ethanol-induced regional and dose-response differences in multiple-unit activity in rabbits. *Psychopharmacology (Berl), 49*(3), 235-244.

Knopfel, T., Vranesic, I., Staub, C., & Gahwiler, B. H. (1991). Climbing Fibre Responses in Olivo-cerebellar Slice Cultures. II. Dynamics of Cytosolic Calcium in Purkinje Cells. *Eur J Neurosci, 3*(4), 343-348.

Knowles, S. K., & Duka, T. (2004). Does alcohol affect memory for emotional and non-emotional experiences in different ways? *Behav Pharmacol, 15*(2), 111-121.

Konnerth, A., Dreessen, J., & Augustine, G. J. (1992). Brief dendritic calcium signals initiate long-lasting synaptic depression in cerebellar Purkinje cells. *Proc Natl Acad Sci U S A, 89*(15), 7051-7055.

Kumar, S., Porcu, P., Werner, D.F., Matthews, D.B., Diaz-Granados, J.L., Helfand, R.S. & Morrow, A.L. (2009). The role of GABAa receptors in the acute and chronic effects of ethanol: a decade of progress. *Psychopharmacology, 205*, 529-564.

LaBar, K. S., & Cabeza, R. (2006). Cognitive neuroscience of emotional memory. *Nat Rev Neurosci, 7*(1), 54-64.

Lamont, M. G., & Weber, J. T. (2012). The role of calcium in synaptic plasticity and motor learning in the cerebellar cortex. *Neurosci Biobehav Rev, 36*(4), 1153-1162. doi: 10.1016/j.neubiorev.2012.01.005

Land, C. & Spear, N. E. (2004). Fear conditioning is impaired in adult rats by ethanol doses that do not affect periadolescents. *Int J Dev Neurosci, 22,* 355-362.

Lavond, D. G., & Steinmetz, J. E. (1989). Acquisition of Classical-Conditioning without Cerebellar Cortex. *Behav Brain Res, 33*(2), 113-164. doi: 10.1016/S0166-4328(89)80047-6

Lee, H., Roh, S., & Kim, D. J. (2009). Alcohol-induced blackout. *Int J Environ Res Public Health, 6*(11), 2783-2792. doi: 10.3390/ijerph6112783

Leitz, J. R., Morgan, C. J., Bisby, J. A., Rendell, P. G., & Curran, H. V. (2009). Global impairment of prospective memory following acute alcohol. *Psychopharmacology (Berl), 205*(3), 379-387. doi: 10.1007/s00213-009-1546-z

Liang, J., Suryanarayanan, A., Chandra, D., Homanics, G. E., Olsen, R. W., & Spigelman, I. (2008). Functional consequences of GABAA receptor alpha 4 subunit deletion on synaptic and extrasynaptic currents in mouse dentate granule cells. *Alcohol Clin Exp Res, 32*(1), 19-26. doi: 10.1111/j.1530-0277.2007.00564.x

Lister, R. G., Gorenstein, C., Risher-Flowers, D., Weingartner, H. J., & Eckardt, M. J. (1991). Dissociation of the acute effects of alcohol on implicit and explicit memory processes. *Neuropsychologia, 29*(12), 1205-1212. doi: http://dx.doi.org/10.1016/0028-3932(91)90034-6

Lovinger, D. M., White, G., & Weight, F. F. (1989). Ethanol inhibits NMDA-activated ion current in hippocampal neurons. *Science, 243*(4899), 1721-1724.

Lovinger, D.M., White, G., & Weight, F.F. (1990). NMDA receptor-mediated synaptic excitation selectively inhibited by ethanol in hippocampal slice from adult rat. *J Neurosci, 10*, 1372-1379.

Ludwig, N., Fox, S. E., Kubie, J. L., Altura, B. M., & Altura, B. T. (1998). Application of the combined single-cell recording/intracerebral microdialysis method to alcohol research in freely behaving animals. *Alcohol Clin Exp Res, 22*, 41-50.

Lye, R. H., Oboyle, D. J., Ramsden, R. T., & Schady, W. (1988). Effects of a Unilateral Cerebellar Lesion on the Acquisition of Eye-Blink Conditioning in Man. *J Physiol-London, 403*, P58-P58.

Mangieri, R.A., Cofresi, R.U. & Gonzales, R.A. (2012). Ethanol seeking by Long Evans rats is not always a goal-directed behavior. PLoS One.

Maren, S. & Fanselow, M. S. (1997). Electrolytic lesions of the fimbria/fornix, dorsal hippocampus, or entorhinal cortex produce anterograde deficits in contextual fear conditioning in rats. *Neurobiol Learn Mem, 67*, 142-149.

Maren, S. (2008). Pavlovian fear conditioning as a behavioral assay for hippocampus and amygdale: cautions and caveats. *Eur J Neurosci, 28*, 1661-1666.

Marr, D. (1971). Simple Memory: A theory for archicortex. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 262, 23-81.

Martin, L. J., Zurek, A. A., Bonin, R. P., Oh, G. H. T., Kim, J. H., Mount, H. T. J., & Orser, B. A. (2011). The sedative but not the memory-blocking properties of ethanol are modulated by a5-subunit-containing g-aminobutyric acid Type A receptors. *Behav Brain Res, 217*, 379-385.

Matthews, D. B. & Best, P. J. (1995). Fimbria/fornix lesions facilitate the learning of a non-spatial response task. *Psychon B Rev, 2*, 113-116.

Matthews, D. B. & Best, P. J. (1997). Evidence for the flexible use of spatial knowledge in the rat. *Psychobiology*, 25, 294-302

Matthews, D. B., Ilgen, M., White, A. M. & Best, P. J. (1999). Acute ethanol administration impairs spatial performance while facilitating nonspatial performance in rats. *Neurobiol Learn Mem*, 72, 169-179.

Matthews, D. B., Morrow, A. L., Tokunaga, S. & McDaniel, J. R. (2002). Acute ethanol administration and acute allopregnanolone administration impair spatial memory in the Morris water task. *Alcohol Clin Exp Res*, *26*, 1747-1751

Matthews, D. B., Simson, P. E. & Best, P. J. (1995). Acute ethanol impairs spatial memory but not stimulus/response memory in the rat. *Alcohol Clin Exp Res*, *19*, 902-909.

Matthews, D. B., Simson, P. E. & Best, P. J. (1996). Ethanol alters spatial processing of hippocampal place cells: A mechanism for impaired navigation when intoxicated. *Alcohol Clin Exp Res*, *20*, 404-407.

McCormick, D. A., & Thompson, R. F. (1984). Neuronal responses of the rabbit cerebellum during acquisition and performance of a classically conditioned nictitating membrane-eyelid response. *J Neurosci*, *4*(11), 2811-2822.

McEchron, M. D. & Disterhoft, J. F. (1999). Hippocampal encoding of non-spatial trace conditioning. *Hippocampus*, *9*, 385-396.

McGlinchey, R. E., Fortier, C. B., Capozzi, S. M., & Disterhoft, J. F. (2005). Trace eyeblink conditioning in abstinent alcoholic individuals: effects of complex task demands and prior conditioning. *Neuropsychology, 19*(2), 159-170. doi: 10.1037/0894-4105.19.2.159

McGlinchey-Berroth, R., Cermak, L. S., Carrillo, M. C., Armfield, S., Gabrieli, J. D., & Disterhoft, J. F. (1995). Impaired delay eyeblink conditioning in amnesic Korsakoff's patients and recovered alcoholics. *Alcohol Clin Exp Res*, *19*(5), 1127-1132.

McKoon, G., & Ratcliff, R. (1979). Priming in episodic and semantic memory. *Journal of Verbal Learning and Verbal Behavior, 18*(4), 463-480. doi: http://dx.doi.org/10.1016/S0022-5371(79)90255-X

Medina, J. F., Nores, W. L., & Mauk, M. D. (2002). Inhibition of climbing fibres is a signal for the extinction of conditioned eyelid responses. *Nature, 416*(6878), 330-333. doi: 10.1038/416330a

Melchior, C. L., Glasky, A. J. & Ritzmann, R. F. (1993). A low dose of ethanol impairs working memory in mice in a win-shift foraging paradigm. *Alcohol*, *10*, 491-493.

Melia, K. R., Ryabinin, A. E., Corodimas, K. P., Wilson, M. C., & LeDoux, J. E. (1996). Hippocampal-dependent learning and experience-dependent activation of the hippocampus are preferentially disrupted by ethanol. *Neuroscience, 74*(2), 313-322. doi: http://dx.doi.org/10.1016/0306-4522(96)00138-8

Mello, N.K. (1971). Alcohol effects on delayed matching to sample performance by rhesus monkey. Psychology & Behavior, 7, 77-101.

Mello, N. K. (1972). Behavioural studies of alcoholism. In: Kissin B, Begleiter H (eds) Biology of alcoholism. Plenum Press, New York, pp 219-291.

Mihalek, R.M., Bowers, B.J., Wehner, J.M., Kralic, J.E., VanDoren, M.J., Morrow, A.L. & Homanics, G.E. (2001). GABAa-receptor δ subunit knockout mice have multiple defects in behavioral responses to ethanol. Alcoholism: Clinical and Experimental Research, 25, 1708-1718.

Mihalek, R.M., Banergee, P.K., Korpi, E.R., Quinlan, J.J., Firestone, L.L., Mi, Z.P., Lagenaur, C., Tretter, V., Sieghart, W., Anagnostaras, S.G., Sage, J.R., Fanselow, M.S., Guidotti. A., Spigelman, I. Li, Z., Delorey, T.M., Olsen, R.W. & Homanics, G.E. (1999). Attenuated sensitivity to neuroactive steroids in gamma-aminobutyrate type A receptor delta subunit knockout mice. Proceedings of the National Academy of Sciences, 96, 12905-12910.

Miller, E.K. & Cohen, J.D. (2001). An integrative theory of prefrontal cortex function. Annu Rev Neurosci, 24, 167-202.

Milton, A.L. & Everitt, B.J. (2010). The psychological and neurochemical mechanism of drug memory reconsolidation: implications for the treatment of addiction. Eur J Neurosci, 31, 2308-2319.

Milton, A.L. & Everitt, B.J. (2012). The persistence of maladaptive memory: Addiction, drug memories and anti-relapse treatments. *Neuro Biobeh Rev*, 36, 1119-1139.

Mishkin, M. (1978). Memory in monkeys severely impaired by combined but not by separate removal of amygdala and hippocampus. Nature, 273, 297-298.

Mizumori, S.J., McNaughton, B.L., Barnes, C.A. & Fox, K.B. (1989). Preserved spatial coding in hippocampal CA1 pyramidal cells during reversible suppression of CA3c output: evidence for pattern completion in hippocampus. Journal of Neuroscience, 9, 3915-3928.

Monk, R. L., & Heim, D. (2013). A critical systematic review of alcohol-related outcome expectancies. *Subst Use Misuse, 48*(7), 539-557. doi: 10.3109/10826084.2013.787097

Moore, M. D., Cushman, J., Chandra, D., Homanics, G. E., Olsen, R. W., & Fanselow, M. S. (2010). Trace and contextual fear conditioning is enhanced in mice lacking the α4 subunit of the GABAA receptor. *Neurobiol Learn Mem, 93*(3), 383-387. doi: http://dx.doi.org/10.1016/j.nlm.2009.12.004

Morris, R. G., Anderson, E., Lynch, G. S., & Baudry, M. (1986). Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. *Nature, 319*(6056), 774-776. doi: 10.1038/319774a0

Morris, R. G. M. (1981). Spatial localization does not require the presence of local cues. *Learn Memory, 12*, 239-260.

Morris, R. G. M., Garrud, P. Rawlins, J. N. P. & O'Keefe, J. (1982). Place navigation impaired in rats with hippocampal lesions. *Nature, 297*, 681-683.

Morrow, A. L., Khisti, R., Tokunaga, S., McDaniel, J. R. & Matthews, D. B. (2003). GABAergic neuroactive steroids modulate selective ethanol actions: Mechanisms and significance. In *Neurosteroid Effects in the Central Nervous System* (pp. 219-245). CRC Press.

Morrow, A. L., Suzdak, P.D. & Paul, S.M. (1987). Steroid hormone metabolites potentiate GABA receptor-mediated chloride ion flux with nanomolar potency. *Eur J Pharmacol, 142*, 483-485.

Moscovitch, M. (1992). Memory and working-with-memory: A component process model based on modules and central systems. J Cog Neuro, 4, 257-267.

Moyer, J. R., Deyo, R. A. & Disterhoft, J.F. (1990). Hippocampectomy disrupts trace eye-blink conditioning in rabbits. *Behav Neurosci*, *104*, 243-252.

Mueller, C., Lisman, S., & Spear, N. (1983). Alcohol enhancement of human memory: Tests of consolidation and interference hypotheses. *Psychopharmacology (Berl), 80*(3), 226-230. doi: 10.1007/BF00436158

Munoz, B., Fritz, B.M., Yin, F. & Atwood, B.K. (2018). Alcohol exposure disrupts mu opioid receptor-mediated long-term depression at insular cortex inputs to dorsolateral striatum, Nature Communications, 9, 1 – 13.

Murray, E. A., & Wise, S. P. (2010). What, if anything, can monkeys tell us about human amnesia when they can't say anything at all?. *Neuropsychologia*, *48*(8), 2385-405.

Novier, A., Diaz-Granados, J.L. & Matthews, D.B. (2015). Alcohol use across the lifespan: An analysis of adolescent and aged rodents and humans. Pharm Biochem Beh, 133, 65-82.

O'Brian, C. P., Childress, A. R., Ehrmann, R., & Robbins, S.J. (1998). Conditioning factors in drug abuse: can they explain compulsions? *J Psychopharmacol, 12*, 15-22.

O'Dell, Alomary, A.A., Vallee, M., Koob, G.F., Fitzgerald, R.L. & Purdy, R.H. (2004). Ethanol-induced increases in neuroactive steroids in the rat brain and plasma are absent in adrenalectomized and gonadectomized rats. European Journal of Pharmacology, 484, 241-274.

O'Keefe, J. & Dostrovsky, J. (1971). The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely moving rat. *Brain Res, 34*, 171-175.

O'Keefe, J. & Nadel, L. (1978). *The Hippocampus as a Cognitive Map*. Oxford: Clarendon Press.

O'Keefe, J. & Speakman A. (1987). Single unit activity in the rat hippocampus during a spatial memory task. *Exp Brain Res, 68,* 1-27.

O'Tousa, D. & Grahame, N. (2014). Habit Formation: Implications for Alcoholism Research. *Alcohol*, 48, 327-335.

Oddie, S. D. & Bland, B. H. (1998). Hippocampal formation theta activity and movement selection. *Neurosci Biobehav R, 22*, 221-231.

Olton, D. S. (1983). Memory functions and the hippocampus. In W. Seifert, *Neurobiology of the Hippocampus*, New York: Academic Press.

Oscar-Berman, M., & Marinković, K. (2007). Alcohol: Effects on Neurobehavioral Functions and the Brain. *Neuropsychol Rev, 17*(3), 239-257. doi: 10.1007/s11065-007-9038-6

Packard, M. G., Hirsh, R., & White, N. M. (1989). Differential effects of fornix and caudate nucleus lesions on two radial maze tasks: Evidence for multiple memory systems. *J Neurosci, 9*, 1465-1472.

Palfai, T. P., & Ostafin, B. D. (2003). The influence of alcohol on the activation of outcome expectancies: the role of evaluative expectancy activation in drinking behavior. *J Stud Alcohol, 64*(1), 111-119.

Parker, E. S., Birnbaum, I. M., Weingartner, H., Hartley, J. T., Stillman, R. C., & Wyatt, R. J. (1980). Retrograde enhancement of human memory with alcohol. *Psychopharmacology (Berl), 69*(2), 219-222. doi: 10.1007/BF00427653

Parker, E. S., Morihisa, J. M., Wyatt, R. J., Schwartz, B. L., Weingartner, H., & Stillman, R. C. (1981). The alcohol facilitation effect on memory: a dose-response study. *Psychopharmacology (Berl), 74*(1), 88-92. doi: 10.1007/BF00431763

Pauli, J., Wilce, P., & Bedi, K. S. (1995). Acute exposure to alcohol during early postnatal life causes a deficit in the total number of cerebellar Purkinje cells in the rat. *J Comp Neurol, 360*(3), 506-512. doi: 10.1002/cne.903600311

Paulus, M. P., Tapert, S. F., Pulido, C., & Schuckit, M. A. (2006). Alcohol Attenuates Load-related Activation During a Working Memory Task: Relation to Level of Response to Alcohol. *Alcohol Clin Exp Res, 30*(8), 1363-1371. doi: 10.1111/j.1530-0277.2006.00164.x

Pedersen, S. L., Treloar, H. R., Burton, C. M., & McCarthy, D. M. (2011). Differences in implicit associations about alcohol between blacks and whites following alcohol administration. *J Stud Alcohol Drugs, 72*(2), 270-278.

Perrett, S. P., Ruiz, B. P., & Mauk, M. D. (1993). Cerebellar cortex lesions disrupt learning-dependent timing of conditioned eyelid responses. *J Neurosci, 13*(4), 1708-1718.

Peterson, J. B., Rothfleisch, J., Zelazo, P. D., & Pihl, R. O. (1990). Acute alcohol intoxication and cognitive functioning. *J Stud Alcohol, 51*(2), 114-122.

Phillips, R. G. & LeDoux, J. E. (1992). Differential contribution of amygdale and hippocampus to cued and contextual fear conditioning. *Behav Neurosci, 106*, 274-285.

Phillips, S. C. & Cragg, B. G. (1984). Alcohol withdrawal causes a loss of cerebellar Purkinje cells in mice. *J Stud Alcohol, 45*(6), 475-480.

Quertemont, E., Grant, K. A., Correa, M., Arizzi, M. N., Salamone, J. D., Tambour, S., . . . Diana, M. (2005). The Role of Acetaldehyde in the Central Effects of Ethanol. *Alcohol Clin Exp Res, 29*(2), 221-234. doi: 10.1097/01.ALC.0000156185.39073.D2

Rabinowitz, A., Cohen, S. J., Finn, D. A., & Stackman, R. W. (2014). The neurosteroid allopregnanolone impairs object memory and contextual fear memory in male C57BL/6J mice. *Horm Behav, 66*, 238-246.

Ramachandran, B., Ahmed, S., Zafar, N., & Dean, C. (2015). Ethanol inhibits long-term potentiation in hippocampal CA1 neurons, irrespective of lamina and stimulus strength, through neurosteroidogenesis. *Hippocampus, 25*(1), 106-118.

Ray, S., Mun, E. Y., Buckman, J. F., Udo, T., & Bates, M. E. (2012). Memory for emotional picture cues during acute alcohol intoxication. *J Stud Alcohol Drugs, 73*(5), 718-725.

Renteria, R., Baltz, E.T. & Gremel, C.M. (2018). Chronic alcohol exposure disrupts top-down control over basal ganglia action selection to produce habits. Nature Communications, 9, 1-11.

Ribeiro, A. M., Barbosa, F. F., Munguba, H., Costa, M. S. M. O., Cavalcante, J. S., & Silva, R. H. (2011). Basolateral amygdala inactivation impairs learned (but not innate) fear response in rats. *Neurobiol Learn Mem, 95*(4), 433-440. doi: http://dx.doi.org/10.1016/j.nlm.2011.02.004

Roediger, H. L. (1990). Implicit memory: Retention without remembering. *Am Psychol, 45*(9), 1043-1056. doi: 10.1037/0003-066X.45.9.1043

Roehrich, L. & Goldman, M. S. (1995). Implicit priming of alcohol expectancy memory processes and subsequent drinking behavior. *Exp Clin Psychopharmacol, 3*(4), 402-410.

Rogers, T.D., Dickson, P.E., Heck, D.H., Goldowitz, D. Mittleman, G., Blaha, C.D. Connecting the dots of the cerebro-cerebellar role in cognitive function: neuronal pathways for cerebellar modulation of dopamine release in the prefrontal cortex. Synapse, 65, 1204-1212.

Ross, W. N. & Werman, R. (1987). Mapping calcium transients in the dendrites of Purkinje cells from the guinea-pig cerebellum in vitro. *J Physiol, 389*, 319-336.

Rossetti, Z. L., Carboni, S., Stancampiano, R., Sori, P., Pepeu, G. & Fadda, F. (2002). Bidirectional modulation of spatial working memory by ethanol. *Alcohol Clin Exp Res, 26*, 181-184.

Rudy, R.W. & Sutherland, R.J. (1995). Configural association theory and the hippocampal formation: An appraisal and reconfiguration. Hippocmapus, 5, 375-389.

Ryabinin, A. E., Miller, M. N., & Durrant, S. (2002). Effects of acute alcohol administration on object recognition learning in C57BL/6J mice. *Pharmacology Biochemistry and Behavior, 71*(1–2), 307-312. doi: http://dx.doi.org/10.1016/S0091-3057(01)00661-X

Ryabinin, A. E. (1995). Alcohol selectively attenuates stress-induced c-fos expression in rat hippocampus. *J Neurosci, 15*, 721-730.

Ryabinin, A. E. (1998). Role of hippocampus in alcohol-induced memory impairment: implications from behavioral and immediate early gene studies. *Psychopharmacology, 139*, 34-43.

Ryabinin, A. E., Criado, J. R., Henriksen, S. J., Bloom, F. E., & Wilson, M. C. (1997). Differential sensitivity of c-Fos expression in hippocampus and other brain regions to moderate and low doses of alcohol. *Molecular Psychiatry, 2*, 32-43.

Sanna, E., Talani, G., Busonero, F., Pisu, M. G., Purdy, R. H., Serra, M. et al. (2004). Brain steroidogenesis mediates ethanol modulation of GABAa receptor activity in rat hippocampus. *J Neurosci, 24*, 6521-6530.

Saults, J. S., Cowan, N., Sher, K. J., & Moreno, M. V. (2007). Differential effects of alcohol on working memory: Distinguishing multiple processes. *Exp Clin Psychopharmacol, 15*(6), 576-587. doi: 10.1037/1064-1297.15.6.576

Schmahmann, J.D. (2004). Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. J Neuropsychiatry Clin Neurosci, 16, 367-378.

Schonewille, M., Gao, Z., Boele, H. J., Veloz, M. F., Amerika, W. E., Simek, A. A., . . . De Zeeuw, C. I. (2011). Reevaluating the role of LTD in cerebellar motor learning. *Neuron, 70*(1), 43-50. doi: 10.1016/j.neuron.2011.02.044

Schweizer, T. A. & Vogel-Sprott, M. (2008). Alcohol-impaired speed and accuracy of cognitive functions: a review of acute tolerance and recovery of cognitive performance. *Exp Clin Psychopharmacol, 16*(3), 240-250. doi: 10.1037/1064-1297.16.3.240

Schweizer, T. A., Vogel-Sprott, M., Danckert, J., Roy, E. A., Skakum, A., & Broderick, C. E. (2006). Neuropsychological profile of acute alcohol intoxication during ascending and descending blood alcohol concentrations. *Neuropsychopharmacol, 31*(6), 1301-1309. doi: 10.1038/sj.npp.1300941

Scoville, W. B. & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosur Ps, 20*, 11-21.

Shimizu, K., Matsubara, K., Uezono, T., Kimura, K., & Shiono, H. (1998). Reduced dorsal hippocampal glutamate release significantly correlates with the spatial memory deficits produced by benzodiazepines and ethanol. *Neuroscience, 83*, 701-706.

Silvers, J. M., Tokunaga, S., Mittleman, G., O'Buckley, T., Morrow, A. L. & Matthews, D. B. (2006). Chronic intermittent ethanol exposure during adolescence reduces the effect of ethanol challenge on hippocampal allopregnanolone levels and Morris water maze task performance. *Alcohol, 39*, 151-158.

Skelton, R. W. (1988). Bilateral cerebellar lesions disrupt conditioned eyelid responses in unrestrained rats. *Behav Neurosci, 102*(4), 586-590.

Söderlund, H., Grady, C. L., Easdon, C., & Tulving, E. (2007). Acute effects of alcohol on neural correlates of episodic memory encoding. *NeuroImage, 35*(2), 928-939. doi: http://dx.doi.org/10.1016/j.neuroimage.2006.12.024

Söderlund, H., Parker, E. S., Schwartz, B. L., & Tulving, E. (2005). Memory encoding and retrieval on the ascending and descending limbs of the blood alcohol concentration curve. *Psychopharmacology (Berl), 182*(2), 305-317.

Solomon, P. R., Stowe, G. T., & Pendlbeury, W. W. (1989). Disrupted eyelid conditioning in a patient with damage to cerebellar afferents. *Behav Neurosci, 103*(4), 898-902.

Solomon, P. R., Vander Schaaf, E. R., Thompson, R. F., Weisz, D. J. (1986). Hippocampus and trace conditioning of the rabbit's classically conditioned nictitating membrane response. *Behav Neurosci, 100*, 729-744.

Sparks, F. T., Spanswick, S. C., Lehmann, H. & Sutherland, R. J. (2013). Neither time nor number of context-shock pairings affect long-term dependence of memory on hippocampus. *Neurobiol Learn Mem, 106*, 309-315.

Squire, L.R. (2004). Memory systems of the brain: a brief history and current perspective. Neurobiol Learn Mem, 82, 171-177.

Stacy, A. W. (1997). Memory activation and expectancy as prospective predictors of alcohol and marijuana use. *J Abnorm Psychol, 106*(1), 61-73. doi: 10.1037/0021-843X.106.1.61

Stanton, M. E., & Goodlett, C. R. (1998). Neonatal ethanol exposure impairs eyeblink conditioning in weanling rats. *Alcohol Clin Exp Res, 22*(1), 270-275.

Staresina, B.P., Michelmann, S., Bonnefond, M., Jensen, O., Axmacher, N. & Fell, J. (2016). Hippocampal pattern completion is linked to gamma power increases and alpha power decreases during recollection. eLife, 5, e17397.

Stell, B.M., Brickley, S.G., Tang, C.Y., Farrant, M. & Mody, I. (2003). Neuroactive steroids reduce neuronal excitability by selectively enhancing tonic inhibition mediated by δ subunit-containing GABAA receptors. PNAS, 100, 14439-14444.

Strick, P. L., Dum, R. P., & Fiez, J. A. (2009). Cerebellum and nonmotor function. *Annu Rev Neurosci, 32*, 413-434. doi: 10.1146/annurev.neuro.31.060407.125606

Su, L. D., Sun, C. L., & Shen, Y. (2010). Ethanol acutely modulates mGluR1-dependent long-term depression in cerebellum. *Alcohol Clin Exp Res, 34*(7), 1140-1145. doi: 10.1111/j.1530-0277.2010.01190.x

Sun, L. W. (2012). Transsynaptic tracing of conditioned eyeblink circuits in the mouse cerebellum. *Neuroscience, 203*, 122-134. doi: 10.1016/j.neuroscience.2011.12.017

Swartzwelder, N.A., Risher, M.L., Abdelwahab, S.H., D'Abo, A., Rezvani, A.H., Levin, E.D., Wilson, W.A. & Swartzwelder, H.S. (2012). Effects of ethanol, Delta-Tetrahydrocannabinol, or their combination on object recognition memory and object preference in adolescent and adult male rats. *Neurosci Lett, 527*, 11-15.

Tabert, M. H., Borod, J. C., Tang, C. Y., Lange, G., Wei, T. C., Johnson, R., . . . Buchsbaum, M. S. (2001). Differential amygdala activation during emotional decision and recognition memory tasks using unpleasant words: an fMRI study. *Neuropsychologia, 39*(6), 556-573.

Tanchuck-Nipper, M.A., Ford, M.M., Hertzberg, A., Beadles-Bohling, A., Cozzoli, D.K. & Finn, D.A. (2015). Sex differences in ethanol's anxiolytic effect and chronic ethanol withdrawal severity in mice with a Null Mutation of the 5α-Reductase type 1 gene. Behavior Genetics, 45, 354-367.

Thompson, R. F. (1986). The neurobiology of learning and memory. *Science, 233*(4767), 941-947.

Thompson, R. F. (1990). Neural mechanisms of classical conditioning in mammals. *Philos Trans R Soc Lond B Biol Sci, 329*(1253), 161-170. doi: 10.1098/rstb.1990.0161

Thompson, R. F. & Kim, J. J. (1996). Memory systems in the brain and localization of memory. *Proc Natl Acad Sci U S A, 93*, 13438-13444.

Tipps, M. E., Raybuck, J. D., Buck, K. J., & Lattal, K. M. (2015). Acute ethanol withdrawal impairs contextual learning and enhances cued learning. *Alcohol Clin Exp Res, 39*(2), 282-290. doi: 10.1111/acer.12614

Tokunaga, S., McDaniel, J. R., Morrow, A. L. & Matthews, D. B. (2003). Effect of acute ethanol administration and acute allopregnanolone administration on spontaneous hippocampal pyramidal cell neural activity. *Brain Res, 967*, 273-280.

Tolman, E. C. (1948). Cognitive maps in rats and men. *Psychological Review, 55*, 189-208.

Topka, H., Valls-Sole, J., Massaquoi, S. G., & Hallett, M. (1993). Deficit in classical conditioning in patients with cerebellar degeneration. *Brain, 116 ( Pt 4)*, 961-969.

Tulving, E. (1972). Episodic and semantic memory. In *Organization of Memory. London: Academic* (pp. 381-403). New York & London: Academic Press.

Urrutia, A. & Gruol, D. L. (1992). Acute alcohol alters the excitability of cerebellar Purkinje neurons and hippocampal neurons in culture. *Brain Res, 569*(1), 26-37.

Valenzuela, C. F., Lindquist, B., & Zamudio-Bulcock, P. A. (2010). A Review of Synaptic Plasticity at Purkinje Neurons with a Focus on Ethanol-Induced Cerebellar Dysfunction. *Functional Plasticity and Genetic Variation: Insights into the Neurobiology of Alcoholism, 91*, 339-372. doi: Doi 10.1016/S0074-7742(10)91011-8

Van Skike, C. E., Botta, P., Chin, V. S., Tokunaga, S., McDaniel, J. M., Venard, J., . . . Matthews, D. B. (2010). Behavioral effects of ethanol in cerebellum are age dependent: potential system and molecular mechanisms. *Alcohol Clin Exp Res, 34*(12), 2070-2080. doi: 10.1111/j.1530-0277.2010.01303.x

VanDoren, M. J., Matthews, D. B., Janis, G. C., Grobin, A. C., Devaud, L. L., & Morrow, A. L. (2000). Neuroactive steroid 3a-Hydroxy-5a-Pregnan-20-One modulates electrophysiological and behavioral actions of ethanol. *J Neurosci, 20*, 1982-1989.

Vasiliou, V. & Pappa, A. (2000). Polymorphisms of human aldehyde dehydrogenases. Consequences for drug metabolism and disease. *Pharmacology, 61*(3), 192-198. doi: 28400

Wagner, J. L., Klintsova, A. Y., Greenough, W. T., & Goodlett, C. R. (2013). Rehabilitation Training Using Complex Motor Learning Rescues Deficits in Eyeblink Classical Conditioning in Female Rats Induced by Binge-Like Neonatal Alcohol Exposure. *Alcohol Clin Exp Res, 37*(9), 1561-1570. doi: 10.1111/Acer.12122

Wall, T. L., Peterson, C. M., Peterson, K. P., Johnson, M. L., Thomasson, H. R., Cole, M., & Ehlers, C. L. (1997). Alcohol Metabolism in Asian-American Men with Genetic Polymorphisms of Aldehyde Dehydrogenase. *Annals of Internal Medicine, 127*(5), 376-379. doi: 10.7326/0003-4819-127-5-199709010-00007

Wallace, M. J., Newton, P. M., Oyasu, M., McMahon, T., Chou, W.-H., Connolly, J., & Messing, R. O. (2006). Acute Functional Tolerance to Ethanol Mediated by Protein Kinase Cε. *Neuropsychopharmacol, 32*(1), 127-136.

Warburton, E.C. & Brown, M.W. (2015). Neural circuitry for rat recognition memory. *Behav Brain Res, 285*, 131-139.

Weissenborn, R. & Duka, T. (2003). Acute alcohol effects on cognitive function in social drinkers: their relationship to drinking habits. *Psychopharmacology (Berl), 165*(3), 306-312. doi: 10.1007/s00213-002-1281-1

Weitemier, A. Z. & Ryabinin, A. E. (2003). Alcohol-induced memory impairments in trace fear conditioning: A Hippocampus-specific effect. *Hippocampus, 13*, 305-315.

Werner, D. F., Blednov, Y. A., Ariwodola, O. J., Silberman, Y., Logan, E., Berry, R. B., … Homanics, G. E. (2006). Knockin mice with ethanol-insensitive alpha1-containing gamma-aminobutyric acid type A receptors display selective alterations in behavioral responses to ethanol. *J Pharmacol Exp Ther, 319*(1), 219-27.

Werner, D.F., Porcu, P., Boyd, K.N., O'Buckley, T.K, Carter, J.M., Kumar, S & Morrow, A.L. (2016). Ethanol-induced GABAA receptor alpha4 subunit plasticity involves phosphorylation and neuroactive steroids. *Molecular and Cellular Neuroscience*, 72, 1-8.

Wetherill, R. R., & Fromme, K. (2011). Acute alcohol effects on narrative recall and contextual memory: an examination of fragmentary blackouts. *Addict Behav, 36*(8), 886-889. doi: 10.1016/j.addbeh.2011.03.012

Wetherill, R. R., Schnyer, D. M., & Fromme, K. (2012). Acute alcohol effects on contextual memory BOLD response: differences based on fragmentary blackout history. *Alcohol Clin Exp Res, 36*(6), 1108-1115. doi: 10.1111/j.1530-0277.2011.01702.x

Whissell, P.D., Eng, D., Lecker, I., Martin, L., Wang, D.S. & Orser, B.A. (2013). Acutely increasing δGABAA receptor activity impairs memory and inhibits synaptic plasticity in the hippocampus. Frontiers in Neural Circuits, 7, 1-12.

White, A. M. & Best, P. J. (2000). Effects of ethanol on hippocampal place-cell and interneuron activity. *Brain Res, 876*, 154-165.

White, A. M., Elek, T. M., Beltz, T. L., & Best, P. J. (1998). Spatial performance is more sensitive to ethanol than nonspatial performance regardless of cue proximity. *Alcohol Clin Exp Res, 22*, 2102-2107.

White, A. M., Simson, P. E., & Best, P. J. (1997). Comparison between the effects of ethanol and diazepam on spatial working memory in the rat. *Psychopharmacology, 133*, 256-261.

Wiers, R. W., van Woerden, N., Smulders, F. T., & de Jong, P. J. (2002). Implicit and explicit alcohol-related cognitions in heavy and light drinkers. *J Abnorm Psychol, 111*(4), 648-658.

Wiltgen, B. J., Sanders, M. J., Ferguson, C., Homanics, G. E., & Fanselow, M. S. (2005). Trace fear conditioning is enhanced in mice lacking the delta subunit of the GABAA receptor. *Learn Mem, 12*(3), 327-333. doi: 10.1101/lm.89705

Wright, J. W., Masino, A. J., Reichert, J. R., Turner, G. D., Meighan, S. E., Meighan, P. C., & Harding, J. W. (2003). Ethanol-induced impairment of spatial memory and brain matrix metalloproteinases. *Brain Res, 963*, 252-261.

Wright, M.W., Glavis-Bloom, C. & Taffe, M.A. (2013). Acute ethanol reduces reversal cost in discrimination learning by reducting perseverance in adolescent rhesus macaques. Alcoholism: Clinical and Experimental Research, 37, 952-960.

Yoshimasu, K., Mure, K., Hashimoto, M., Takemura, S., Tsuno, K., Hayashida, M., . . . Miyashita, K. (2015). Genetic alcohol sensitivity regulated by ALDH2 and ADH1B polymorphisms is strongly associated with depression and anxiety in Japanese employees. *Drug Alcohol Depend, 147*, 130-136. doi: 10.1016/j.drugalcdep.2014.11.034

Yin, H.H., Knowlton, B.J., Balleine, B.W. (2005a). Blockade of NMDA receptors in the dorsomedial striatum prevents action-outcome learning in instrumental conditioning, European Journal of Neuroscience, 22, 505-512.

Yin, H.H., Ostlund, S.B., Knowlton, B.J. & Balleine, B.W. (2005b). The role of the dorsomedial striatum in instrumental conditioning. European Journal of Neuroscience, 22, 513-523

Yu, S. Y., Gao, R., Zhang, L., Luo, J., Jiang, H., & Wang, S. (2013). Curcumin ameliorates ethanol-induced memory deficits and enhanced brain nitric oxide synthase activity in mice. *Prog Neuro-Psychoph, 44*, 210-216. doi: http://dx.doi.org/10.1016/j.pnpbp.2013.03.001

Yuzaki, M. (2013). Cerebellar LTD vs. motor learning-lessons learned from studying GluD2. *Neural Netw, 47*, 36-41. doi: 10.1016/j.neunet.2012.07.001

Zamudio-Bulcock, P.A., Homanics, G.E. & Woodward, J.J. (2018). Loss of ethanol inhibition of N-Methl-D-Aspartate Receptor-mediated currents and plasticity of cerebellar synapses in mice expressing the GluN1(F639A) subunit. Alcoholism: Clinical and Experimental Research, 42, 698-705.

Zhang, Y., Yu, J., Li., W., Yang, Y., Wang, X. & Qian, Z. (2016). Effect of acute ethanaol administration on the hippocampal region neural activity using a microelectrode array. Alcohol Clin Exp Res, 40, 1857-1864.

Zorumski, C. F., Mennerick, S., & Izumi, Y. (2014). Acute and chronic effects of ethanol on learning-related synaptic plasticity. *Alcohol*, *48*, 1-17.

Table 1. Effects of ethanol on brain region dependent tasks.

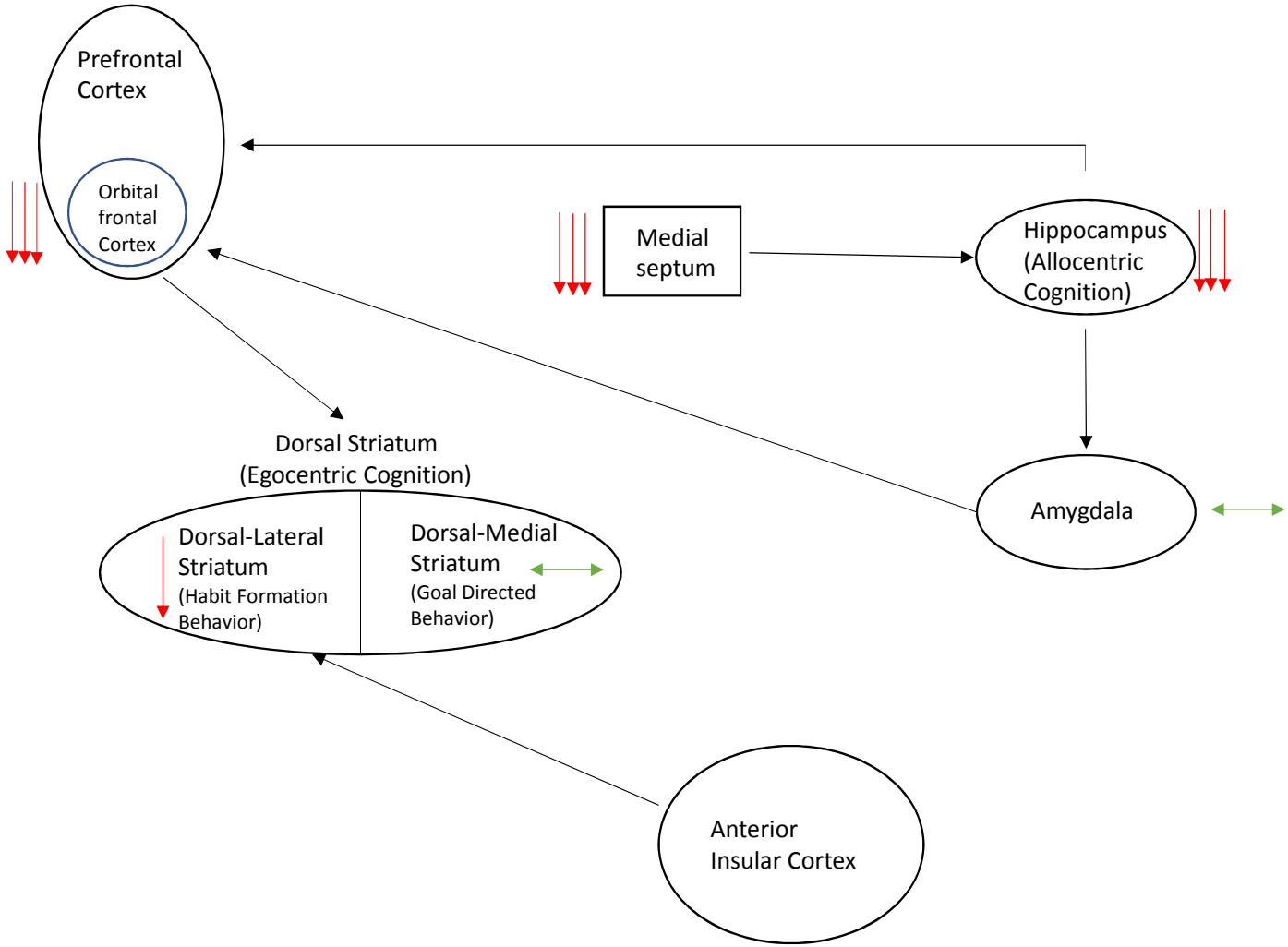
| Brain Region | Task | Effective Doses | Effect of Acute Alcohol | Citations |
|---|---|---|---|---|
| **Hippocampus** | Spatial Working Memory | 0.5 g/kg, i.p. | Low dose facilitation under challenging task conditions | Rossetti et al., 2002 |
| | | 0.75 - 2.0 g/kg, i.p. | Otherwise, dose-dependent impairments | Hoffmann & Matthews, 2001; Givens 1995 |
| | Spatial Reference Memory | 1.5 - 2.0 g/kg, i.p. | Dose-dependent impairments | Matthews et al., 1995; 2002; Shimizu et al., 1998; Wright et al., 2003 |
| | Contextual Learning and Memory | 0.8 - 1.6 g/kg, i.p. | Impairs contextual learning and memory when administered before training or testing | Devenport & Carter, 1986; Melia et al., 1996; Weitemier & Ryabinin, 2003 |
| | Trace Conditioning | 0.8 - 2.5 g/kg, i.p./i.g. | Impairs trace conditioning when administered before or after training (with a long trace), but not before testing | Hunt et al., 2009; Land & Spear, 2004; Weitemier & Ryabinin, 2003 |
| | Spontaneous Alternation | 2.0 g/kg, i.p. | Inhibits spontaneous alternation | Cox, 1970 |
| | Novel Object Recognition | 2.4 g/kg, i.p. in C57BL/6J mice 1.0 g/kg, i.p. in Kun Ming mice | Impairs novel object recognition when administered before training, but not after | Ryabinin et al., 2002; Yu et al., 2013 |
| | Long-term potentiation in vitro | 5-100 mM | Inhibits and blocks LTP | Blitzer et al., 1990; Lovinger et al., 1989, 1990 |
| | Place cell specificity in vivo | 1.0 - 2.0 g/kg, i.p. | Disrupts spatial specificity of place cells in awake, freely behaving rats | Matthews et al., 1996; White & Best, 2000 |
| **Cerebellum** | Eyeblink conditioning | 0.375 g/kg i.g. | Low doses facilitate conditioned responding | Hernandez & Powell, 1986 |
| | | 0.75 – 1.5 g/kg i.g | Dose-dependent inhibition at moderate to high doses | Hernandez et al., 1986; Hobson, 1966 |
| | | 0.75 g/kg i.g. | Delays extinction | Hernandez et al., 1986 |

| | | | | |
|---|---|---|---|---|
| | Long-term depression | 10-80 mM | Dose-dependent inhibition | Belmeguenai et al., 2008; He et al., 2013 |
| **Amygdala** | Cued conditioning | 1.0 – 1.5 g/kg, i.p | Pre-training ethanol impairs cued responding | Gulick & Gould, 2008 |
| | | 0.25 g/kg, i.p. | Post-training low-dose ethanol enhances cued responding | Gulick & Gould, 2008 |
| | | 0.25 – 1.5 g/kg i.p. | No effect when administered during testing | Gould 2003; Gulick & Gould, 2007 |
| | Emotional memory recall | 0.65 g/kg p.o. | Anterograde impairment | Knowles & Duka, 2004 |
| | | 0.65 g/kg p.o. | Retrograde facilitation | Knowles & Duka, 2004 |

Table 2. Effects of acute ethanol on human memory

| Memory Store | Task | Effective BAC/dose | Effect of Acute Alcohol | Citations |
|---|---|---|---|---|
| **Short term memory** | Working memory | 70-90 mg/dL | Impairs working memory capacity | Finn et al., 1999 |
| | | 65 mg/dL | Greater working memory impairment in older participants compared to adults | Boissoneault et al., 2014 |
| | | 68-80 mg/dL | Acute functional tolerance develops to ethanol induced increases in reaction time, but not error rates | Grattan-Miscio & Vogel-Sprott, 2005 |
| | Visual-spatial working memory | 90-80 mg/dL | Impairs visual-spatial working memory performance during the descending limb of BAC curve | Schweizer et al., 2006 |
| | | 59-65 mg/dL | No effect on visual spatial working memory | Paulus et al., 2006; Weissenborn & Duka, 2003 |
| **Implicit long term memory** | Backwards reading and word completion | 0.3-0.6 g/kg | No impairment of implicit memory when words were learned during intoxication | Lister et al., 1991 |
| | Priming | 75-80 mg/dL | Implicit alcohol expectancies are not changed in moderate drinkers | Pedersen et al., 2011 |
| | | 40 mg/dL | Increased implicit association toward positive alcohol outcomes in risky drinkers | Palfai & Ostafin, 2003 |
| **Explicit long term memory** | Blackouts | 70-420 mg/dL | Occurrence of both fragmentary and *en bloc* blackouts increases with increasing BAC | Hartzler & Fromme, 2003 |
| | Recall | 54-70 mg/dL | Impaired intoxicated recall when task was learned while intoxicated | Birnbaum et al., 1978; Lister et al., 1991 |
| | | 70 mg/dL | No effect on intoxicated recall with a long delay after sober learning | Birnbaum et al., 1978 |
| | | 80 mg/dL | Enhanced sober recall after 24h when administered immediately after sober learning | Parker et al., 1980 |
| | Recognition | 34-80 mg/dL | Retroactive enhancement when administered immediately after sober learning | Parker et al., 1980; 1981 |
| | Prospective memory | 0.6 g/kg | Impairs all types of prospective memory | Leitz et al., 2009 |

**Figure 1: Potential Brain Region Schematic Underlying the Cognitive Switch Produced by Acute Ethanol on Cognition.** The red arrows indicate brain regions impacted by acute ethanol exposure while the green arrows indicate brain regions marginally impacted by acute ethanol exposure. The number of red arrows indicate the strength of the impairment in function. As can be seen, acute ethanol exposure strongly impairs the functionality of the medial septum, hippocampus and prefrontal cortex/orbitalfrontal cortex brain regions. This impairment reduces an organisms reliance on allocentric cognition. Concomitantly, acute alcohol produces a smaller impairment in dorsal-lateral striatum function and marginal effects in both dorsal-medial striatum and amygdala function thereby facilitating egocentric cognition. Given the large impairment in the hippocampal/prefrontal cortex system and smaller impairments in the striatal system, acute ethanol exposure can set up an "addiction memory" by facilitating a switch to habit based behavior (dorsal-lateral striatum) based on specific cues (doral-medial striatum) function.



Highlights

Ethanol has selective impairments on learning and memory
Ethanol facilitates a cognitive switch from goal directed to habit directed memory